Analyse des paramètres oncologiques des patients pris en charge en réhabilitation améliorée après chirurgie

Fatah Tidadini

THESE de DOCTORAT DE
L'UNIVERSITE CLAUDE BERNARD DE LYON 1

Ecole Doctorale N° 205
INTERDISCIPLINAIRE SCIENCES-SANTE

Discipline: Recherche clinique

Soutenue publiquement le 13/12/2022, par :

Fatah TIDADINI

Analyse des paramètres oncologiques des patients pris en charge en réhabilitation améliorée après chirurgie

Devant le jury composé de :

GLEHEN Olivier	PU-PH - Université de Lyon	Président du jury
GERMAIN Adeline	PU-PH - Université de Lorraine	Rapporteur
LAKKIS Zaher	PU-PH - Université de Franche-Comté	Rapporteur
DUCHALAIS Emilie	PH - CHU de Nantes	Examinatrice
MALGRAS Brice	Médecin en Chef Pr Ag - HIA Bégin	Examinateur
ARVIEUX Catherine	PU-PH - Université Grenoble-Alpes	Directrice de thèse
FAUCHERON Jean-Luc	PU-PH - Université Grenoble-Alpes	Directeur de thèse

UNIVERSITE CLAUDE BERNARD - LYON 1

Président de l'Université	**M. le Professeur Frédéric FLEURY**
Président du Conseil Académique	M. le Professeur Hamda BEN HADID
Vice-président du Conseil d'Administration	M. le Professeur Didier REVEL
Vice-président de la Commission formation	Mme la Professeure Céline BROCHIER
Directeur Général des Services	M. Pierre ROLLAND

COMPOSANTES SANTE

Faculté de Médecine Lyon Est – Claude Bernard	Directeur : M. le Professeur G.RODE
Faculté de Médecine et de Maïeutique Lyon Sud – Charles Mérieux	Directrice : Mme la Professeure P. PAPAREL
Faculté d'Odontologie	Directeur : M. le Professeur JC. MAURIN
Institut des Sciences Pharmaceutiques et Biologiques	Directeur : M. le Professeur C. DUSSART
Institut des Sciences et Techniques de la Réadaptation	Directeur : M. le Professeur J. LUAUTE

COMPOSANTES ET DEPARTEMENTS DE SCIENCES ET TECHNOLOGIE

Faculté Biosciences	Directrice : Mme la Professeure K. GIESELER
Faculté des Sciences	Directeur : M. le Professeur B. ANDRIOLETTI
Département GEP	Directrice : Mme la Professeure R. FERRIGNO
Département Informatique	Directrice : Mme S. BOUAKAZ-BRONDEL
Département Mécanique	Directeur : M. le Professeur M. BUFFAT
UFR Sciences et Techniques des Activités Physiques et Sportives	Directeur : M. le Professeur G. BODET
Observatoire des Sciences de l'Univers de Lyon	Directeur : M. B. GUIDERDONI
Polytech Lyon	Directeur : M. le Professeur E.PERRIN
Institut Universitaire de Technologie de Lyon 1	Directeur : M. le Professeur M. MASSENZIO
Ecole Supérieure du Professorat et de l'Education	Directeur : M. le Professeur P. CHAREYRON
Institut de Science Financière et d'Assurances	Directeur : M. N. LEBOISNE

TITRE : Analyse des paramètres oncologiques des patients pris en charge en réhabilitation améliorée après chirurgie.

RESUME :

La réhabilitation améliorée après chirurgie (RAC) cancérologique digestive prend une place de plus en plus importante dans le parcours de soin et connaitre l'impact de cette prise en charge à long terme est primordial pour les cliniciens. Nous avons souhaité analyser les paramètres oncologiques des patients pris en charge en mode RAC pour la chirurgie colo-rectale mini-invasive et la chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC). Sur le plan clinique, nous avons réalisé deux études évaluant le lien entre le protocole RAC, les facteurs de risque et la survie à 3 ans après chirurgie colorectale mini-invasive et quatre autres évaluant les bénéfices et risques de la PIPAC dans le traitement de la carcinose péritonéale. Sur le plan méthodologique, nous avons analysé les biais apparus lors de nos travaux et proposé des outils d'amélioration pour la mise en œuvre de futures études cancérologiques dans cette population. Nos résultats ont montré que la pratique de la RAC après chirurgie colorectale est efficace aussi bien chez les patients jeunes que chez les patients âgés de 65 ans et plus. L'analyse de la survie à 3 ans par un modèle de Cox multivarié a identifié le groupe RAC comme un facteur protecteur avec une réduction de 30 % du risque de décès, indépendamment des facteurs de risque classiques identifiés. Nos études sur la PIPAC ont montré que cette thérapie pourrait retarder la progression oncologique, améliorer la survie par rapport à la chimiothérapie systémique sans PIPAC et réduire la durée totale des hospitalisations, sans impact négatif sur la qualité de vie du patient. Sur le plan économique, la valorisation de l'hospitalisation pour la réalisation de ce traitement reste insuffisante par rapport au coût réel engendré (61 %). Sur le plan pharmacologique, la PIPAC à base d'Oxaliplatine a été identifiée comme facteur de risque associé à plus de douleur post-opératoire par rapport à la PIPAC à base de l'association Doxorubicine-Cisplatine. L'identification des biais méthodologiques a permis de proposer des outils d'amélioration dans la mise en œuvre des études cliniques dans ces deux populations. Pour évaluer l'impact de la RAC et de la PIPAC à long terme, nous proposons de réaliser des études de cohortes prospectives et multicentriques, avec des analyses appariées selon des facteurs pronostiques identifiés. Nos travaux apportent des éléments pouvant permettre de diminuer la morbi-mortalité et améliorer la qualité de vie des patients et de leurs proches aidants.

MOTS CLES :
Cancer colorectal, carcinose péritonéale, réhabilitation améliorée après chirurgie (RAC), chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC), survie globale, facteurs de risques

TITLE : Analysis of oncological parameters in patients treated with enhanced recovery after surgery protocol

ABSTRACT

The enhanced recovery after surgery (ERAS) protocol is taking an increasingly important place in the care pathway after digestive oncology interventions. Knowing the long-term impact of this protocol is essential for clinicians. Our initial objective was to analyze the oncological parameters of patients receiving the ERAS protocol after minimally invasive colorectal surgery and pressurized intraperitoneal aerosol chemotherapy (PIPAC). At the clinical level we carried out two studies evaluating the link between the ERAS protocol, risk factors and 3-year survival after minimally invasive colorectal surgery and four studies evaluating the benefits and risks of PIPAC in the treatment of peritoneal carcinomatosis. At the methodological level, we analyzed the biases that appeared during our work and propose tools for improvements in the implementation of future cancer studies in this population. Our results showed that the ERAS protocol after colorectal surgery is effective both in younger patients and in patients aged 65 and over. The analysis of 3-year survival using a multivariate Cox model identified ERAS as being a protective factor with a 30% reduction in the risk of death, independently of the classical risk factors. Our studies on PIPAC have shown that this therapy could delay oncological progression, improve survival compared to systemic chemotherapy alone and reduce the total duration of hospitalizations, without negative impact on the patient's quality of life. From an economic point of view, the current valuation of hospitalization for this treatment remains insufficient (only 61% of the cost) compared to the real cost to the hospital. Pharmacologically, PIPAC using oxaliplatin was associated with more postoperative pain compared to PIPAC using a combination of doxorubicin and cisplatin. The identification of methodological biases make it possible to propose tools for improving the design of clinical studies in these two populations. To assess the impact of ERAS and PIPAC in the long term we propose to carry out prospective and multicenter cohort studies, analyzing groups of patients that are matched according to identified prognostic factors. Our work provides elements that can help reduce morbidity and mortality and improve the quality of life of patients and their caregivers.

KEY WORDS: colorectal cancer, peritoneal carcinomatosis, enhanced recovery after surgery (ERAS), pressurized intraperitoneal aerosol chemotherapy (PIPAC), overall survival, risk factors

INTITULE ET ADRESSE DE L'UNITE OU DU LABORATOIRE :

Université Claude Bernard Lyon 1

EMR HCL-UCBL1 3738 « Centre pour l'Innovation en Cancérologie de Lyon, CICLY »

UFR Faculté de Médecin Lyon-Sud-Charles Mérieux BP12

165 Chemin du Grand Revoyet

69921 OULLINS Cedex

REMERCIEMENTS

A l'ensemble des membres de mon jury de thèse,

Madame le Professeur Catherine ARVIEUX, Monsieur le Professeur Jean-Luc FAUCHERON, de m'avoir proposé ce travail et associé à vos thématiques de recherche. Merci d'avoir accepté d'encadrer ce travail, pour votre disponibilité et soutien tout au long de ces trois années.

Monsieur le Professeur Olivier GLEHEN, de m'avoir accueilli dans son équipe (centre d'innovation en cancérologie de Lyon) et d'avoir accepté la présidence de cette thèse.

Madame le Professeur Adeline GERMAIN, Monsieur le Professeur Zaher LAKKIS pour avoir accepté d'être les rapporteurs de ce travail.

Monsieur le Médecin en Chef Professeur agrégé Brice MALGRAS pour avoir accepté de participer à mon jury.

Madame le Docteur Emilie DUCHALAIS pour avoir accepté de participer à mon jury.

Madame le Professeur Cécile BRIGAND et Monsieur le Professeur Gaëtan GAVAZZI pour avoir accepté de participer à mon comité de suivi individuel et de m'avoir accompagné dans ce travail.

Monsieur Jean-Louis QUESADA, Madame le Docteur Alison FOOTE, Monsieur le Docteur Laurent VILLENEUVE, de m'avoir accompagné dans ce travail.

A toute l'équipe du service de Chirurgie Digestive et de l'Urgence du CHU Grenoble-alpes.

A toute ma famille et mes amis.

A LA MEMOIRE

De mes parents,

De mon frère Salem,

De tous mes proches qui nous ont quittés.

TABLE DES MATIERES

TABLE DES FIGURES

LISTE DES ANNEXES

LISTE DES ABREVIATIONS

ASA	American Society of Anesthesiologists
CCAM	Classification Commune des Actes Médicaux
CHIP	Chimiothérapie hyperthermique Intra-Péritonéale
CHU	Centre Hospitalier Universitaire
CHUGA	Centre Hospitalier Universitaire Grenoble-Alpes
CP	Carcinose Péritonéale
CCR	Cancer Colorectal
DFS	Disease-Free Survival
ERAS	Enhanced Recovery After Surgery
EVA	Echelle Visuelle Analogique
GRACE	Groupe francophone de Réhabilitation Améliorée après Chirurgie
HIA	Hôpital d'Instruction des Armées
HR	Hazard Ratio
ICER	Rapport Coût Efficacité Différentiel
NHS	National Health Service
ONLY_CHEM	Chimiothérapie systémique seule
OS	Overall survival
PCI	Peritoneal Cancer Index
PIPAC C/D	PIPAC à base de l'association Doxorubicine-Cisplatine
PIPAC Ox	PIPAC à base d'Oxaliplatine
PIPAC	Chimiothérapie Intrapéritonéale Pulvérisée par Aérosols
PIPAC_CHEM	PIPAC associé à une chimiothérapie systémique
PMSI	Programme de Médicalisation des Systèmes d'Information
PMSI-MCO	Programme de Médicalisation des Systèmes d'Information, Médecine, Chirurgie et Obstétrique
Pre-ERAS	Prise en charge conventionnelle
QALY	Quality-Adjusted Life Year
R0	Résection radicale
RAC	Réhabilitation Améliorée après Chirurgie
RC	Recherche Clinique
RENAPE	Réseau National du Péritoine
SFAR	Société Française d'Anesthésie et de Réanimation
SFCD	Société Française de Chirurgie Digestive
SG	Survie Globale
VAS	Visual analogue Score

I. INTRODUCTION

La fréquence des cancers digestifs a beaucoup augmenté au cours des dernières décennies dans le monde. En 2020, 1,93 million nouveaux cas de cancer colorectal (CCR) ont été diagnostiqués et 916 000 décès ont été enregistrés[1,2]. En France, avec 43 336 nouveaux cas et 17 117 décès recensés en 2018, le CCR se situe au troisième rang des cancers les plus fréquents et le deuxième en termes de mortalité par cancer. Huit décès par CCR sur dix surviennent chez les patients de 65 ans et plus[3]. Au 1er janvier 2019, cette tranche d'âge comptait 13,4 millions d'habitants français, soit 20 % de la population[4]. Selon une grande base de données prospective suédoise, 50 % des patients développeront des métastases et environ 9 % développeront une carcinose péritonéale (CP)[5]. La médiane de survie globale (SG) des patients atteints de CCR métastatique s'est considérablement améliorée et est actuellement estimée à 30 mois[6,7].

I.1. Cancer colorectal

Le CCR se développe à partir de cellules initialement normales qui tapissent la paroi interne du colon ou du rectum, se transforment et se multiplient de façon anarchique, jusqu'à former une tumeur maligne[8,9]. Malgré tous les progrès thérapeutiques, les techniques innovantes et les avancées de la recherche, le traitement curatif du CCR fait toujours largement appel à la chirurgie d'exérèse radicale[10,11].

La chirurgie du CCR consiste à réséquer la tumeur avec une marge saine. Le type de chirurgie réalisée dépend du siège de la tumeur sur le cadre colorectal. Le chirurgien résèque également les ganglions lymphatiques de drainage de la tumeur (curage ganglionnaire), qui sont ensuite analysés par un anatomopathologiste pour déterminer s'ils contiennent ou non des cellules cancéreuses[12,13].

La chirurgie colorectale expose les patients à des complications postopératoires fréquentes[14], qui sont associées à une diminution de la survie à long terme[15]. Les patients âgés et fragiles sont plus exposés encore à ces complications[16].

I.2. Carcinose péritonéale

La CP est la dissémination de cellules cancéreuses dans le péritoine. C'est le signe d'une maladie avancée, le plus souvent associée à un pronostic sombre avec une survie de quelques mois[17,18]. Le traitement standard repose sur la chimiothérapie systémique. Cependant, la

pharmacocinétique de la diffusion du médicament dans le péritoine est médiocre, avec une efficacité limitée par rapport aux autres sites métastatiques comme le foie ou le poumon[19]. La chimiothérapie hyperthermique intra-péritonéale (CHIP) a suscité de grands espoirs[20,21], mais une étude récente a finalement montré qu'elle avait une efficacité limitée[22]. Pour les CP non résécables, Reymond et al. ont décrit en 2012, une nouvelle approche, consistant à appliquer des agents de chimiothérapie directement dans le péritoine à l'aide d'un aérosol sous pression, connu sous le nom de chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC)[23].

I.3. Diagnostic et prise en charge

Le diagnostic et la prise en charge de ces cancers sont complexes et nécessitent des équipes multidisciplinaires et complémentaires, faisant intervenir de nombreux spécialistes : hépato-gastro-entérologues, chirurgiens digestifs, oncologues, radiothérapeutes, radiologues, médecins nucléaires, anatomopathologistes et anesthésistes. Le dépistage précoce, les progrès thérapeutiques, les techniques innovantes et la recherche sont des éléments essentiels de l'amélioration de la qualité de la prise en charge des patients ayant un cancer. Un suivi à long terme structuré pourrait également favoriser leur récupération physique et leur intégration psychosociale[24].

La recherche clinique (RC), la réhabilitation améliorée après chirurgie (RAC) et la PIPAC, font chacune partie intégrante des innovations stratégiques, mises en place dans notre établissement pour la prise en charge de ces patients.

I.3.1. Recherche clinique

La recherche clinique est indispensable pour mieux comprendre et/ou mieux traiter les maladies, ainsi que pour identifier les facteurs de risque potentiels[25]. Elle permet aux patients d'avoir accès à des traitements expérimentaux et de nouvelles stratégies thérapeutiques. Cela est peut-être encore plus pertinent quand il s'agit de pathologies où la prise en charge et les perspectives de guérison sont insuffisantes à la vue des connaissances actuelles. En France, la recherche est encadrée par la loi Jardé[26].

La réussite d'une étude clinique repose sur plusieurs conditions et facteurs liés d'une part :

- Au patient
- A la maladie
- A l'acte chirurgical
- Aux ressources humaines et financières dédiées au projet

D'autre part à l'essai clinique lui-même, à savoir :

- L'apport scientifique et l'impact clinique de l'étude proposée
- La méthodologie (choix des objectifs, des critères de jugement, du plan expérimental, des critères d'inclusion et non-inclusion et le nombre d'effectifs)
- La faisabilité et la présence d'études concurrentes dans le service

I.3.2. Réhabilitation améliorée après chirurgie

La récupération précoce des capacités fonctionnelles et organiques après une intervention repose sur plusieurs facteurs liés au patient, à la maladie, aux traitements et surtout au mode organisationnel de la prise en charge postopératoire. L'équipe danoise du Professeur Henrik Kehlet a décrit en 1995, une nouvelle approche de prise en charge des patients après chirurgie colique, connue sous le nom de réhabilitation améliorée après chirurgie[27,28]. Cette innovation stratégique vise à réduire au maximum le stress physique et psychique lié à l'intervention, en prévenant les dysfonctions organiques secondaires de la chirurgie, ce qui permet au patient de récupérer plus vite ses capacités physiologiques (Figure 1).

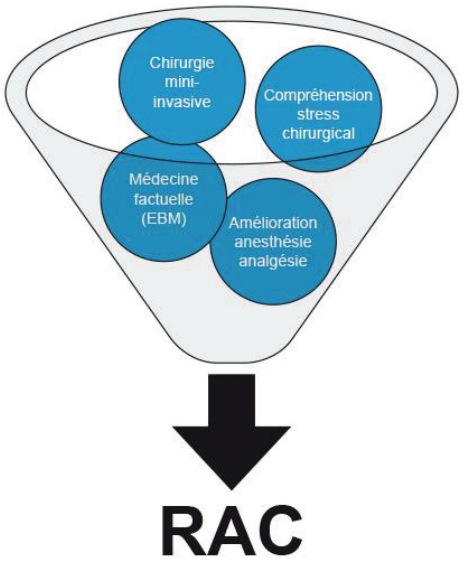


Figure 1 : La réhabilitation améliorée après chirurgie d'après Ouvrage de K. Slim , Elsevier Ed, 2018[29]

Le CHU Grenoble-Alpes (CHUGA) est membre du groupe francophone de réhabilitation améliorée après chirurgie (GRACE - www.grace-asso.fr) et a été pionnier dans la mise en place nationale de la RAC en participant à la création des recommandations de bonnes pratiques[30], présentées en annexe 1. Le CHUGA est labellisé centre expert GRACE. L'engagement de notre Direction dans cette démarche a permis à notre service de mettre en place une stratégie de prise en charge efficace et de qualité, avec un travail d'équipe pluridisciplinaire (chirurgiens, anesthésistes, infirmières de soins et de bloc, stomathérapeutes, diététicienne, hypnothérapeute, kinésithérapeutes, attaché de recherche clinique et secrétaires), notamment par l'élaboration de protocoles de soins et chemins cliniques du programme ainsi que leurs procédures d'évaluation (Figure 2).

I.3.2.1. Bénéfices médicaux et économiques de la RAC

La RAC est un mode de réhabilitation multidisciplinaire qui offre des avantages médicaux et économiques importants. Plusieurs études ont fourni des preuves que cette stratégie thérapeutique peut réduire jusqu'à 50 % les complications péri-opératoires et raccourcit jusqu'à 30 % la durée de séjour à l'hôpital pour la chirurgie colorectale[31,32].

Un autre exemple de l'efficacité de la RAC a été démontré pour la chirurgie hépato-biliaire. Dans une revue systématique des données de 27 articles publiées sur la RAC, 6 essais contrôlés randomisés et 21 études de cohorte de 3739 patients (1777 dans le groupe RAC et 1962 dans le groupe de soins standards), Noba et al. ont conclu que l'introduction des protocoles RAC est sûre et faisable dans les hépatectomies, sans augmenter les taux de mortalité et de réadmission, tout en réduisant la durée de séjour et le risque de complications, et avec des économies importantes sur les coûts hospitaliers[33].

Une autre étude effectuée dans les hôpitaux civils de Lyon a permis une estimation du gain obtenu en termes de dépenses de santé à partir de la réduction de la durée de séjour obtenue après des interventions de chirurgie viscérale et orthopédique. Ces gains cumulés sont supérieurs à 200 000 euros par an la première année soit un gain de 195 euros par séjour pour un peu plus de 1000 séjours. La deuxième année, ces gains s'élèvent à 288 000 euros[34].

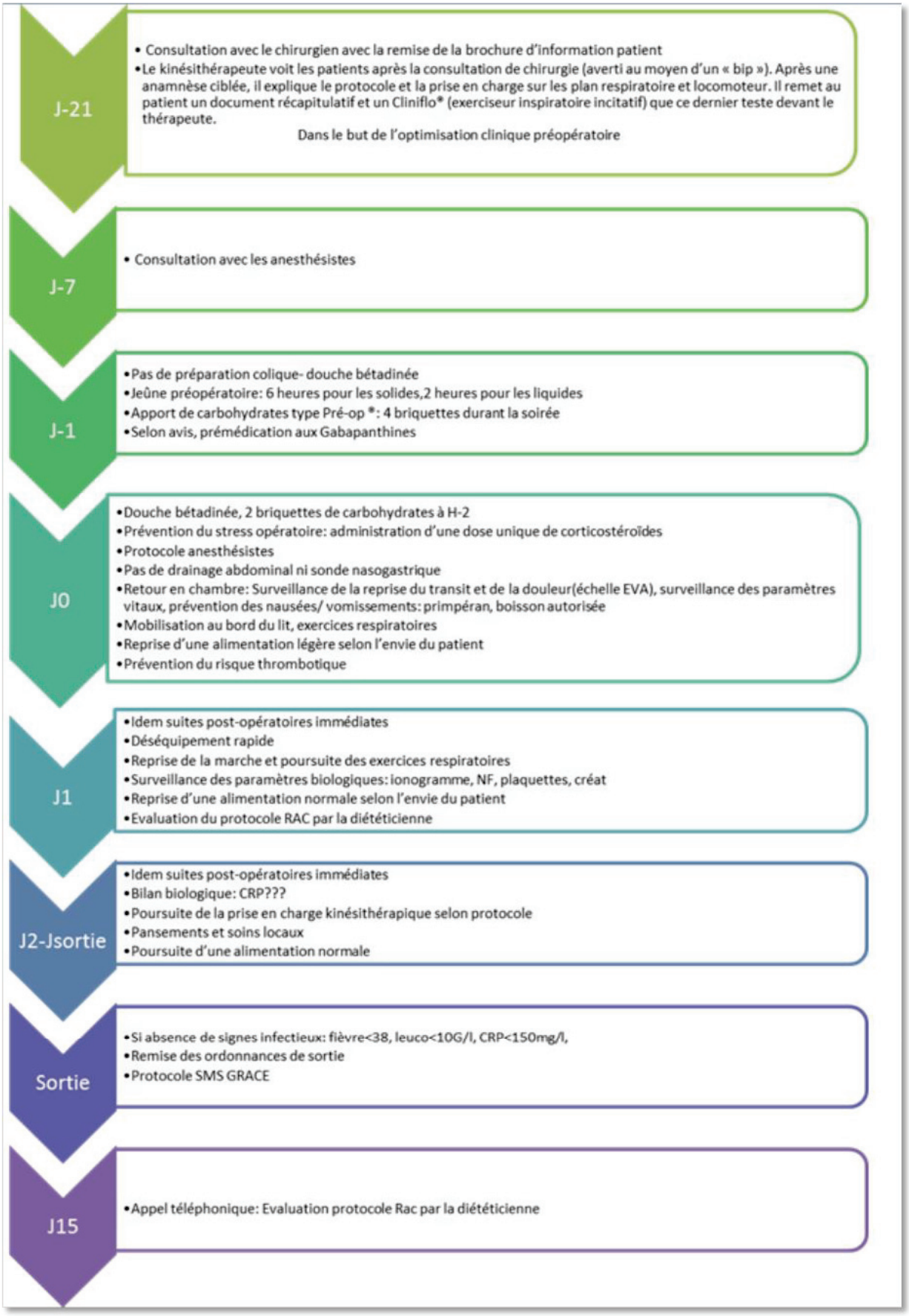


Figure 2 : Protocole de prise en charge RAC en chirurgie digestive – CHU de Grenoble-alpes

I.3.3. Chimiothérapie intrapéritonéale pulvérisée par aérosols

La PIPAC est une nouvelle technique chirurgicale, développée pour le traitement de la carcinose péritonéale initialement non résécable. Elle combine une exploration laparoscopique complète de l'abdomen, une évaluation du peritoneal cancer index (PCI), des biopsies péritonéales, une cytologie en présence d'ascite, avant l'administration d'une chimiothérapie pulvérisée directement dans l'abdomen lors de la cœlioscopie.

Les procédures sont réalisées toutes les 6 à 8 semaines, en alternance avec une chimiothérapie systémique, en remplaçant un cycle de chimiothérapie intraveineuse par une PIPAC. L'intérêt de la PIPAC est qu'elle offre un meilleur rendement et une meilleure distribution du médicament dans le tissu péritonéal que par Chimiothérapie Hyperthermique Intra-Péritonéale (CHIP) ou chimiothérapie intraveineuse[35]. La réduction de la dose de chimiothérapie administrée par PIPAC est sept à dix fois moindre par rapport à celle utilisée en intra-veineux, ce qui limite les effets indésirables. La PIPAC a depuis été appliquée au CP de toutes origines[36–43], et réalisées dans plus de 39 pays à travers le monde[44]. Plusieurs études récentes, ont fourni des preuves que le schéma thérapeutique associant PIPAC et chimiothérapie systémique procurait un bénéfice de survie dans le traitement des CP, sans altérer la qualité de vie, voire en l'améliorant[36, 37, 45, 46]. Mais peut de surcroît diminuer le volume de la CP et permettre qu'elle soit résécable et donc accessible à une chirurgie d'exérèse complète[47].

En juillet 2016, l'hôpital Grenoble-alpes est devenu l'un des premiers centres experts dans le traitement de la carcinose péritonéale dans le cadre du Réseau National du Péritoine (RENAPE) à proposer cette technique en France. La procédure chirurgicale est effectuée dans une salle d'opération réservée aux procédures PIPAC et réalisée selon une check liste établie lors de la mise en place du traitement dans notre centre présentée en annexe 2, comme décrite dans la littérature[23,48]. Sous anesthésie générale, une laparoscopie est réalisée en utilisant une technique laparoscopique ouverte. Un pneumopéritoine à 12 mmHg de pression est créé et deux trocarts à ballonnet laparoscopique de 11 et 12 mm sont utilisés. Une exploration complète de l'abdomen, une évaluation du score PCI, des biopsies péritonéales et une cytologie en présence d'ascite sont réalisées avant l'administration de la chimiothérapie. Doxorubicine à la dose de 1,5 mg/m^2 en association avec Cisplatine à la dose de 7,5 mg/m^2

diluées respectivement dans une solution de 40 et 150 ml de chlorure de sodium 0,9 % sont administrées. En cas de contre-indication, l'administration d'Oxaliplatine à la dose de 92 mg/m^2 diluée dans une solution de dextrose 5 % est effectuée (Figure 3 et 4).

Pratiquée dans un nombre limité de centres en France, la PIPAC ne dispose actuellement pas de codage relatif dans la classification commune des actes médicaux (CCAM). Aucune étude française portant sur l'évaluation des coûts hospitaliers de ce traitement n'a été menée à notre connaissance et peu de données économiques sont disponibles sur les coûts de cette chimiothérapie. Au Royaume-Uni, une étude coût-efficacité a été menée (Javanbakht et al., 2021) à partir d'un modèle de Markov : le rapport coût efficacité différentiel (ICER) dans cette étude est estimé à 31 868 £ par année de vie en bonne santé (QALY) gagnée. Cette étude pionnière dans cette indication s'est basée sur de nombreuses sources d'informations disponibles dans les bases de données britanniques : littérature, National Health service (NHS), industriels, British National Formulary[49].

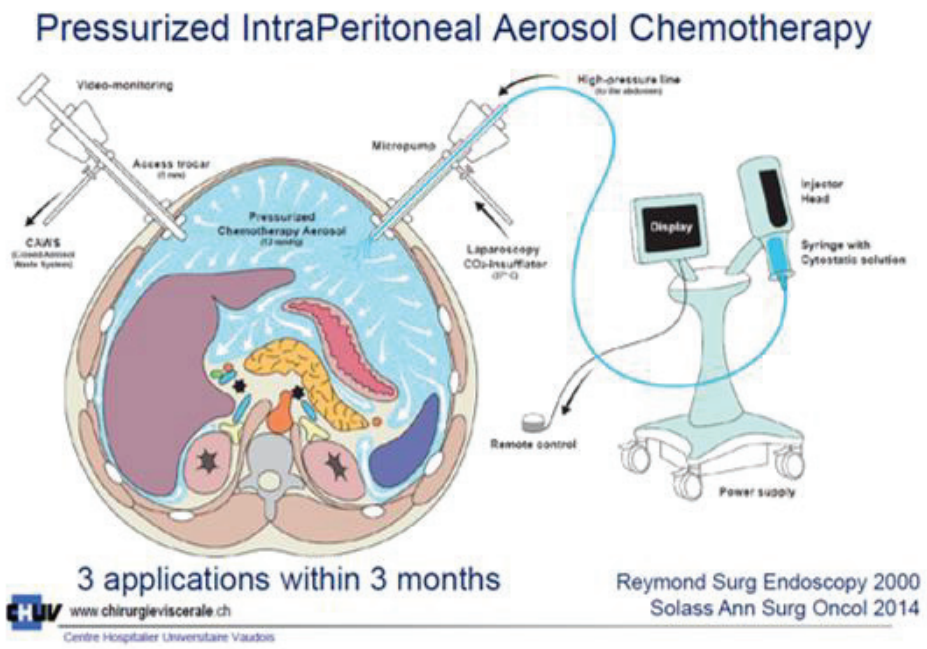


Figure 3 : Technique de la procédure PIPAC, d'après Solass et al.[23]

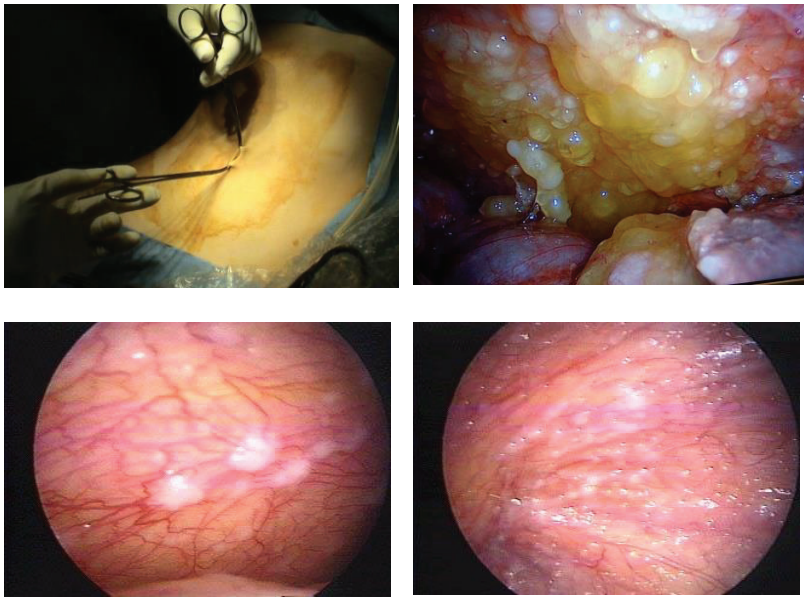


Figure 4 : Vue opératoire : performance de la cœlioscopie dans le diagnostic de la carcinose

II. OBJECTIFS

Nos travaux ont un double objectif, clinique et méthodologique :

1. Sur le plan clinique :
   - Evaluer l'impact du protocole RAC sur l'évolution des paramètres oncologiques et la prise en charge des patients pour la chirurgie colo-rectale mini-invasive et la PIPAC.
   - Evaluer les bénéfices et risques du traitement PIPAC dans le traitement de la carcinose péritonéale.

2. Sur le plan méthodologique :
   - Analyser les biais méthodologiques apparus lors de notre travail.
   - Proposer des outils d'amélioration pour la mise en œuvre des études cancérologiques dans cette population.

Pour répondre à ces questions, nous avons réalisé six études cliniques.

- Effet de la RAC et facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer – cohorte rétrospective de 1001 patients.
- L'association entre le protocole RAC, les facteurs de risque et la survie à 3 ans après chirurgie du CCR chez les personnes âgées - cohorte rétrospective de 650 patients.
- Évaluation de la douleur post-opératoire après PIPAC dans le traitement de la carcinose péritonéale.
- Résultats oncologiques de la PIPAC dans le traitement de la carcinose péritonéale.
- Effet de la PIPAC sur le taux de survie des patients atteints de carcinose péritonéale d'origine gastrique.
- Coût d'une hospitalisation pour PIPAC.

III. LES ETUDES

III.1. Déroulement de la recherche

Dans son déroulement, nous avons structuré notre recherche en deux parties.

Partie 1 : Réhabilitation Améliorée après Chirurgie

La première partie de notre travail a été axée sur l'évaluation de l'impact de la mise en œuvre du programme RAC dans notre service. L'objectif des deux premières études a été d'évaluer l'effet de la mise en œuvre de la RAC et les facteurs de risque sur la survie globale, 3 ans après résection colorectale pour cancer, chez tous nos patients, puis chez les patients âgés de 65 ans et plus. Nous avons ensuite évalué si ce programme était applicable au traitement de la carcinose péritonéale, pathologie sévère, nécessitant une prise en charge et un environnement chirurgical particuliers. Nous avons alors réalisé une évaluation de la douleur post-opératoire après PIPAC.

Partie 2 : Bénéfices et risques de la PIPAC

Dans cette deuxième partie, nous avons évalué l'impact médical et économique de la mise en œuvre du traitement par PIPAC dans notre service. Nous avons étudié les résultats oncologiques de cette chimiothérapie. Nous avons ensuite comparé les résultats de la PIPAC associée à une chimiothérapie systémique (PIPAC_CHEM) à ceux de la chimiothérapie systémique seule (ONLY_PIPAC) chez des patients atteints de CP d'origine gastrique.

La dernière étude a eu pour but de faire une évaluation économique et d'estimer le coût d'une hospitalisation pour PIPAC dans un CHU et un Hôpital d'Instruction des Armées (HIA) français.

III.1.1. Partie 1 : Réhabilitation Améliorée après Chirurgie

1. Effet de la réhabilitation améliorée et facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer – cohorte rétrospective de 1001 patients

Bien que le protocole RAC ait été développé il y a plusieurs années, et que de nombreuses études aient traité de ce thème, dans la littérature, une seule étude rapporte une survie à 3 ans pour les patients RAC[50]. Une étude suédoise a également suggéré qu'une adhésion élevée à la RAC pourrait être associée à une amélioration de la survie à 5 ans[51].

Nous avons donc évalué chez 1001 patients l'effet de la réhabilitation améliorée et les facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer.

RESUME

Introduction : Plusieurs études récentes, ont montré que la réhabilitation améliorée après chirurgie (RAC) réduit la morbi-mortalité et raccourcit la durée du séjour par rapport à la prise en charge conventionnelle (pré-RAC). Le but de cette étude était d'évaluer l'effet de la mise en œuvre de ce protocole sur la SG à 3 ans et les résultats postopératoires chez les patients subissant une résection colorectale pour cancer.

Méthode : Etude rétrospective, monocentrique, comparative et non randomisée. Entre janvier 2005 et décembre 2017, 1001 patients ont été inclus (RAC, n = 497 ; pré-RAC, n = 504).

Résultats : Le taux de SG à 3 ans était significativement meilleur pour les patients RAC (76,1 % vs 69,2 % ; p = 0,017). La durée d'hospitalisation (médiane 10 jours vs 15 ; p = ≤ 0,001) et le taux de réadmission à 90 jours (15 % vs 20 % ; p = 0,037) étaient significativement inférieurs dans le groupe RAC. La survie sans récidive à 3 ans (p = 0,398) et les complications à 90 jours (p = 0,560) étaient similaires dans les deux groupes. L'analyse de la survie à 3 ans par un modèle de Cox multivarié a identifié le groupe RAC comme un facteur protecteur avec une réduction de 30 % du risque de décès : (HR = 0,70 [0,55 - 0,90]).

Conclusion : La mise en place du protocole RAC dans notre service a été associée à une amélioration de la survie à 3 ans, une réduction de la durée d'hospitalisation et du taux de réadmission. La RAC est associée à une meilleure survie à 3 ans, indépendamment des autres paramètres communément considérés. Un score ASA > 2, le tabagisme, des antécédents de cancer et de fibrillation auriculaire sont des facteurs de risque délétères liés à une mortalité précoce.

International Journal of Colorectal Disease
https://doi.org/10.1007/s00384-022-04155-1

ORIGINAL ARTICLE

Effect of implementation of enhanced recovery after surgery (ERAS) protocol and risk factors on 3-year survival after colorectal surgery for cancer–a retrospective cohort of 1001 patients

Fatah Tidadini[1,2] · Aline Bonne[1] · Bertrand Trilling[1] · Jean-Louis Quesada[3] · Pierre-Yves Sage[1] · Alison Foote[1] · Catherine Arvieux[1,2] · Jean-Luc Faucheron[1]

Accepted: 17 April 2022

Abstract

Purpose Several recent studies have shown that the enhanced recovery after surgery (ERAS) protocol reduces morbidity and mortality and shortens the length of stay compared to conventional recovery strategy (pre-ERAS). The aim of this study was to evaluate the effect of the implementation of this protocol on 3-year overall survival and postoperative outcome in patients undergoing colorectal resection for cancer.

Methods This was a retrospective, single-center, comparative, and non-randomized study. Between January, 2005, and December, 2017, 1001 patients were included (ERAS, $n=497$; pre-ERAS, $n=504$).

Results The 3-year overall survival rate was significantly better for ERAS than for pre-ERAS patients (76.1 vs 69.2%; $p=0.017$). The length of hospital stay (median 10 days vs 15; $p=\leq 0.001$) and the 90-day readmission rate (15 vs 20%; $p=0.037$) were significantly lower in the ERAS group. Three-year recurrence-free survival ($p=0.398$) and 90-day complications ($p=0.560$) were similar in the two groups. Analysis of 3-year survival by a multivariate Cox model identified ERAS as a protective factor with a 30% reduction in the risk of death: (HR = 0.70 [0.55–0.90]).

Conclusion The implementation of the ERAS protocol was associated with an improvement in 3-year survival, a reduction of the length of hospital stay and the rate of readmission. ERAS is associated with better 3-year survival, independent of other commonly considered parameters. An ASA score > 2, smoking, a history of cancer, and atrial fibrillation are deleterious risk factors linked to earlier mortality.

Keywords Colorectal cancer · Colorectal resection · Enhanced recovery after surgery (ERAS) · Overall survival · Postoperative complications

Introduction

In 2020, 1.93 million new cases of colorectal cancer were diagnosed and 935,000 deaths were recorded worldwide [1]. Despite the progress made in adjuvant treatments, chemoradiotherapy, and immunotherapy, curative treatment still involves radical excision surgery [2, 3]. Colorectal surgery frequently exposes patients to postoperative complications [4], which are associated with a decrease in long-term survival independently of other commonly considered parameters [5]. The prevention of complications is based on several factors linked to the patient, the disease, the treatments, and especially to the mode of postoperative care. In 1995, the Danish team of Professor Henrik Kehlet described a new approach to the care of patients after colon surgery, known as enhanced rehabilitation after surgery (ERAS) [6, 7]. This multidisciplinary strategy to perioperative care aims to reduce the physical and psychological stress associated with the operation, by preventing organic dysfunctions secondary to surgery, allowing the patient to recover her/his capacities more quickly. Several studies have provided

✉ Jean-Luc Faucheron
JLFaucheron@chu-grenoble.fr

1 Colorectal Unit, Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, CS 10217, 38043 Grenoble, France

2 Lyon Center for Innovation in Cancer, EA 3731, Lyon 1 University, Lyon, France

3 Clinical Pharmacology Unit, INSERM CIC 1406, Grenoble Alpes University Hospital, 38043 Grenoble, France

Published online: 26 April 2022

evidence that this strategy can reduce perioperative complications by up to 50% and shorten the length of hospital stay for colorectal surgery by up to 30% [8–11]. On the basis of these data, we conducted a non-randomized retrospective study comparing the results of enhanced rehabilitation after surgery, following the recommendations of the working group of the French society of anesthesia and resuscitation (SFAR) and the French society of digestive surgery (SFCD) [12], with conventional management (pre-ERAS) in patients who had undergone colorectal resection for cancer at the Grenoble-Alpes University Hospital (France). The main objective was to assess the effect of the implementation of ERAS in our department on overall survival (OS) at 3 years (death from any cause). Secondary objectives were length of hospitalization, 90-day complications, 90-day readmission, and 3-year recurrence-free survival.

Methods

This was a retrospective, single-center, comparative, and non-randomized study, which took place in the digestive surgery and emergency department of Grenoble Alpes University Hospital (France), classed as a reference center for colorectal surgery by the French-speaking group for improved rehabilitation after surgery (GRACE). The study population consisted of all consecutive adult patients, who had undergone resection for colorectal cancer or a precancerous lesion and were cared for using the ERAS protocol or received conventional care (pre-ERAS). The records of consecutive patients recorded in the hospital's electronic medical records (PMSI) between January 2005 and December 2017 were screened. Non-inclusion criteria included patients presenting or developing peritoneal carcinomatosis, patients having resection for palliative reasons, those under curatorship or tutelage, and those with missing data. The allocation of patients in the two groups (ERAS and pre-ERAS) was calculated using January 1, 2012, the date of the official launch of the ERAS program in our department, as the pivotal date. The lesion location was classified as colon and rectum according to the type of surgical resection.

The survival status of the patients was determined by consulting medical records as well as by telephone calls. Overall survival was calculated by the Kaplan–Meier method. The times were calculated from the date of operation. Patient characteristics, disease, and postoperative complications at 90 days were compared.

Postoperative follow-up

After each operation, patients were followed by the surgery department staff with evaluation of the usual clinical and para-clinical parameters. All patients had a postoperative consultation with the surgeon at 1 month and 3 months, and were then followed up every 3 months up to 2 years, then every year for at least 5 years. All postoperative events occurring during the first 90 days (morbidity, rehospitalization reoperation, and death) were recorded, with complications graded according to the Clavien-Dindo classification [13], in which severe complications were grades 3 to 5.

Statistical analysis

Continuous data are presented using descriptive statistics: median and (25th–75th percentiles). Categorical data are presented using numbers and percentages. Quantitative parameters were compared between groups using Mann–Whitney tests due to rejection of normality. Qualitative parameters were compared using the chi-square test if distributed normally, or otherwise using a Fisher's exact test.

Overall survival (OS) was defined as the time between the date of surgery and death due to any cause within the 3-year follow-up period. Survival rates were calculated using the Kaplan–Meier method.

Recurrence-free survival at 3 years by treatment group was compared using a Log-Rank test. Severe complication-free survival at 90 days by treatment group was compared using a Log-Rank test.

The role of confounding factors was explored using a univariate Cox proportional hazards model. A multivariate Cox proportional hazards model, with backward-stepwise selection (and a 15% threshold), was used to evaluate overall survival at 3 years for each treatment group.

A threshold of 5% was used to define the significance of the statistical tests. No adjustment for multiplicity was applied. Statistical analysis was performed using Stata software version 14.2 (STATA, StataCorp, TX, USA).

Results

Characteristics of the study population

Among 1072 patients whose records were consulted, 71 were not included in the study. Consequently, 1001 patients were included in the study (ERAS, $n=497$, or pre-ERAS, $n=504$) (Fig. 1). Demographic and medical data, tumor characteristics, and details of surgery are presented in Tables 1 and 2, respectively. At the time of the operation, the median age was 70 years [61; 78], 628 were men (62.8%), the median body mass index (BMI) was 24.7 [21.9–28.1], 14.9% of patients were obese, and 6% were underweight. The majority of resections involved the colon (62%). The ERAS and pre-ERAS groups appear to be similar in terms of age, sex, BMI, neoadjuvant radiotherapy, and adjuvant chemotherapy.

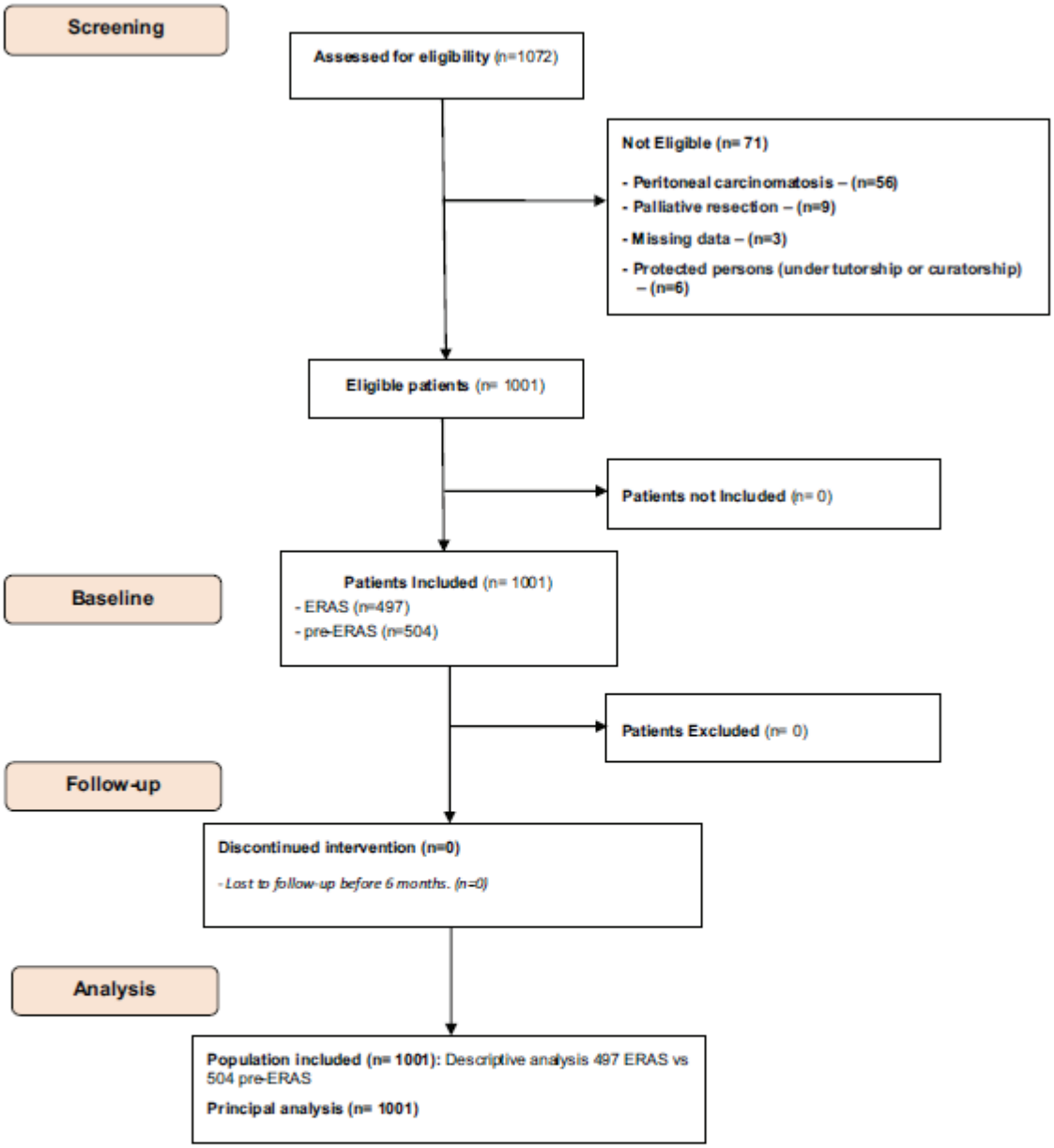


Fig. 1 Study flowchart

In the ERAS group, there were more patients with an American Society of Anesthesiologists (ASA) score > 2 ($p = 0.002$), more patients with a history of arterial hypertension ($p = 0.006$), dyslipidemia ($p = 0.030$), cardiac arrhythmia by atrial fibrillation ($p = 0.028$), deep vein thrombosis or pulmonary embolism ($p = 0.034$), or abdominal surgery ($p \leq 0.001$).

There were significantly more resections of the right transverse colon ($p = 0.004$) and more laparoscopic interventions ($p \leq 0.001$) in the ERAS group.

The ileostomy rate was significantly higher in the ERAS group ($p \leq 0.001$). The operating room occupancy time was significantly higher in this group ($p \leq 0.001$).

Table 1 Demographic and medical characteristics

	Whole population $n=1001$	ERAS $n=497$	Pre-ERAS $n=504$	p-value
Age	70 (61; 78) (19–100)	70 (61; 78) (33–96)	70 (61; 79) (19–100)	0.634[d]
Sex Male Female	628 (62.8%) 372 (37.2%)	319 (64.2%) 178 (35.8%)	309 (61.4%) 194 (38.6%)	0.368[a]
Body mass index (BMI)	24.7 (21.9;28.1) (14.7–52.5)	24.6 (22;28.1) (15–52.5)	24.7 (21.8;28) (14.7–46)	0.854[d]
Obesity (BMI ≥ 30)	127 (14.9%)	73 (15.2%)	54 (14.5%)	0.785[a]
Underweight (BMI < 20)	51 (6%)	28 (5.8%)	23 (6.2%)	0.827[a]
Active smoker	142 (14.2%)	75 (15.1%)	67 (13.3%)	0.415[a]
Chronic obstructive pulmonary disease/respiratory pathology	156 (15.6%)	84 (16.9%)	72 (14.3%)	0.260[a]
Dyslipidemia	198 (19.8%)	112 (22.5%)	86 (17.1%)	**0.030[a]**
Hypertension	426 (42.6%)	233 (46.9%)	193 (38.3%)	**0.006[a]**
Cardiopathy	226 (22.6%)	103 (20.7%)	123 (24.4%)	0.164[a]
Stroke/mini-stroke	68 (6.8%)	38 (7.7%)	30 (6%)	0.287[a]
Atrial fibrillation	100 (10%)	60 (12.1%)	40 (7.9%)	**0.028[a]**
Peripheral artery disease	45 (4.5%)	23 (4.6%)	22 (4.4%)	0.841[a]
Deep vein thrombosis/pulmonary embolism	84 (8.4%)	51 (10.3%)	33 (6.6%)	**0.034[a]**
Diabetes	165 (16.5%)	84 (16.9%)	81 (16.1%)	0.723[a]
Renal failure	90 (9%)	49 (9.9%)	41 (8.1%)	0.340[a]
Hepatopathy	57 (5.7%)	34 (6.8%)	23 (4.6%)	0.120[a]
Abdominal surgery	432 (43.2%)	255 (51.3%)	177 (35.2%)	**≤0.001[a]**
Other cancer	252 (25.4%)	124 (25.2%)	128 (25.6%)	0.871[a]
Other medical history	603 (61%)	305 (61.9%)	298 (60.2%)	0.592[a]
Neoadjuvant radiotherapy	194 (20.3%)	100 (20.8%)	94 (19.8%)	0.700[a]
Adjuvant chemotherapy	241 (25.2%)	127 (26.2%)	114 (24.1%)	0.435[a]
Preoperative characteristics				
Anticoagulants	184 (18.7%)	96 (19.8%)	88 (17.7%)	0.385[a]
Hemoglobin	118 (104; 131)	118 (105; 133)	116 (101; 130)	**0.030[d]**

Mean ± standard deviation and median (25th, 75th percentiles), frequency (number), (min; max)

[a]Chi-2 test

[b]Fisher-exact test

[c]Student t-test

[d]Mann-Whitney test

In the pre-ERAS group, there were significantly more high rectal resections ($p=0.003$) and more laparotomy interventions ($p \leq 0.001$). The rate of delayed colo-anal anastomosis (ACAD) was significantly higher in the pre-ERAS group ($p \leq 0.001$). There were also more patients operated on by senior surgeons in this group ($p \leq 0.001$).

Regarding histological analysis, the percentage of patients with in situ adenocarcinoma was similar in the ERAS and pre-ERAS groups, as was the number of patients with stage 4 adenocarcinoma ($p=0.278$). There was no statistically significant difference in the number of R1 margin resection ($p=0.658$). The number of lymph nodes recovered during lymphadenectomy was significantly higher in the ERAS group ($p=0.008$).

Three-year overall survival

For the whole study population ($n=1001$), the 3-year overall survival rate was (73.1%), but significantly better for patients in the ERAS group than in the pre-ERAS group, respectively (76.1 [72.1–79.7%] vs 69.2% [64.9–73.1%]; $p=0.017$) (Fig. 2). During follow-up, 230 (23.8%) patients were diagnosed with recurrent colorectal cancer, 125 (25.5%) in the ERAS group and 105 (22%) in the pre-ERAS group. The 3-year recurrence-free survival was similar in the two groups: 71.7 [67.2–75.6%] vs 72.8% [68–77%]; $p=0.398$) (e-Fig. 1 in supplement).

Table 2 Tumor characteristics and details of surgery

	Whole population $n=1001$	ERAS $n=497$	Pre-ERAS $n=504$	p-value
Colon*	621 (62%)	317 (63.8%)	304 (60.3%)	0.259[a]
Right colon	323 (32.3%)	156 (31.4%)	167 (33.2%)	0.540[a]
Right transverse colon	59 (5.9%)	40 (8.1%)	19 (3.8%)	**0.004**[a]
Left transverse colon	46 (4.6%)	23 (4.6%)	23 (4.6%)	0.961[a]
Left colon	278 (27.8%)	138 (27.8%)	140 (27.8%)	0.997[a]
Rectum*	380 (38%)	180 (36.2%)	200 (39.7%)	0.259[a]
High rectum	144 (14.4%)	55 (11.1%)	89 (17.7%)	**0.003**[a]
Middle rectum	192 (19.2%)	96 (19.3%)	96 (19.1%)	0.914[a]
Lower rectum	147 (14.7%)	75 (15.1%)	72 (14.3%)	0.719[a]
Tumoral stage (pT)				0.278[a]
0	67 (7.1%)	35 (7.3%)	32 (6.9%)	
1	82 (8.7%)	50 (10.5%)	32 (6.9%)	
2	135 (14.4%)	63 (13.2%)	72 (15.5%)	
3	478 (50.8%)	235 (49.3%)	243 (52.4%)	
4	179 (19%)	94 (19.7%)	85 (18.3%)	
Distant metastasis (M1)	12.7%(118)	12.3%(59)	13%(59)	0.774[a]
Surgical resection				
Resection R1	46 (4.9%)	22 (4.6%)	24 (5.2%)	0.658[a]
Resection R2	9 (1%)	6 (1.3%)	3 (0.7%)	0.506[b]
Number of lymph nodes removed	14 (9; 19) (0–70)	15 (9; 20) (0–48)	13 (8; 18) (0–70)	**0.008**[d]
Number of positive lymph nodes	0 (0; 1) (0–25)	0 (0; 1) (0–22)	0 (0; 1) (0–25)	0.908[d]
Laparoscopy	613 (61.2%)	389 (78.3%)	224 (44.4%)	**≤0.001**[a]
Laparotomy	388 (38.8%)	108 (21.7%)	280 (55.6%)	**≤0.001**[a]
Robot	6 (0.6%)	6 (1.2%)	0 (0%)	**0.015**[b]
Conversion	63 (6.3%)	39 (8%)	24 (4.8%)	**0.039**[a]
Delayed colo-anal anastomosis (ACAD)	58 (5.8%)	14 (2.8%)	44 (8.8%)	**≤0.001**[a]
Ileostomy	190 (19.1%)	120 (24.4%)	70 (13.9%)	**≤0.001**[a]
Associated act	207 (21.3%)	99 (21%)	108 (21.6%)	0.824 [a]
Duration of operation (minutes)	173.5 (123; 241.5) (32–579)	171 (124; 228) (32–532)	180 (122; 250) (65–579)	0.254[d]
Operation room occupation time (minutes)	255.5 (205; 337) (112–640) n=250	273 (210; 347) (120–640) n=180	225 (189; 285) (112–535) n=70	**≤0.001**[d]
Senior surgeon	697 (69.8%)	319 (64.6%)	378 (75%)	**≤0.001**[a]
Junior surgeon (assistant)	302 (30.3%)	176 (35.4%)	126 (25%)	**≤0.001**[a]

Mean ± standard deviation and median (25th, 75th percentiles), frequency (number), (min; max)

*The number of cases does not correspond to the total number of subgroups because some tumors had several locations

[a]Chi-2 test

[b]Fisher-exact test

[c]Student t-test

[d]Mann-Whitney test

Duration of hospitalization

Patients given the ERAS protocol had a shorter hospital stay compared to patients in the pre-ERAS group (median 10 days [7–19] vs 15 [10–23]; $p=\leq 0.001$) (e-Table 1 in supplement).

90-day re-admission rate

The 90-day readmission rate was significantly different between ERAS and pre-ERAS patients: 74/493 (15% [12–18.5]) vs 101/504 (20% [16.6–23.8]); $p=0.037$ (e-Table 2 in supplement).

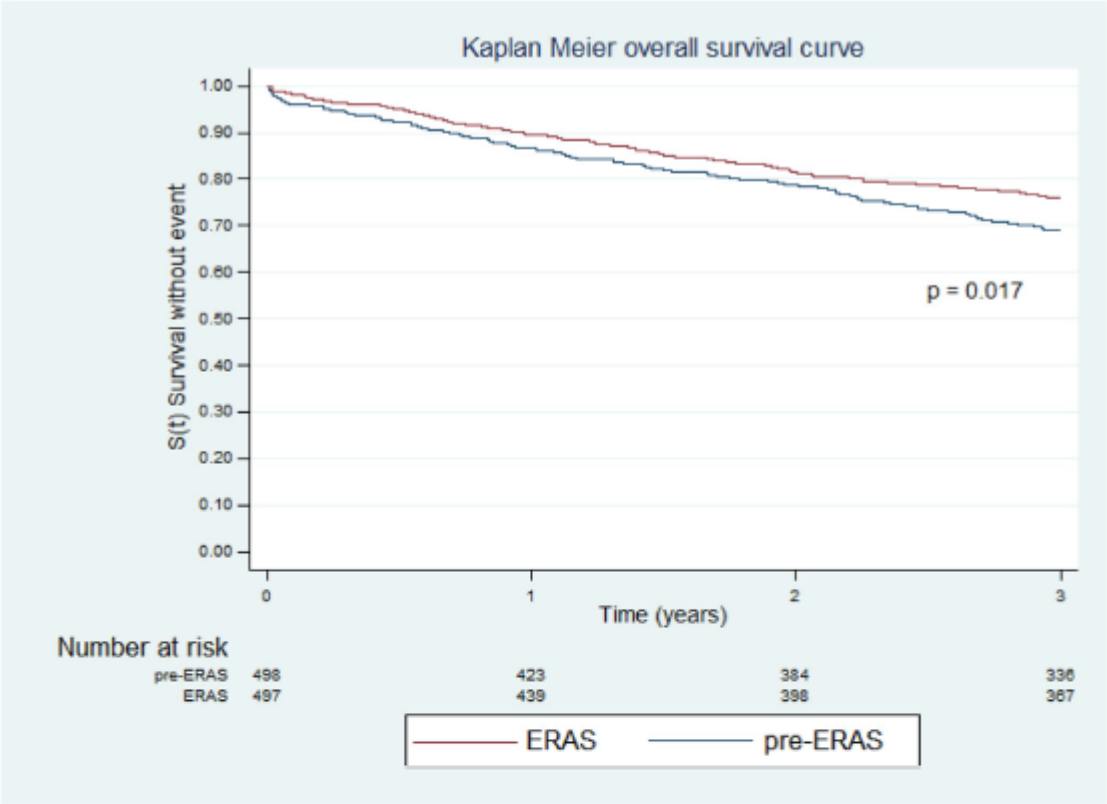


Fig. 2 Kaplan–Meier overall survival curve up to 3 years after surgery

Post-operative complications at 90 days

The rates of postoperative complications at 90 days were similar in the two groups: 266 (53.5%) vs 279 (55.4%); $p=0.560$. More postoperative nasogastric intubations due to ileus (NGT ileus) were needed in the ERAS group: 35 (7%) vs 20 (4%) cases; $p=0.033$. Severe complications (Clavien-Dindo ≥ 3) at 90 days were also similar between ERAS and pre-ERAS patients: 100 (20.1%) vs 92 (18.3%), respectively; $p=0.453$, as was the rate of all-cause mortality of 4.4% (3.6 vs 5.2%; $p=0.236$) (Table 3).

Multivariate analysis

We looked for confounding factors on which it would be interesting to adjust the comparison of 3-year survival between groups. Univariate analyses using a Cox model showed that age (hazard ratio (HR) 1.44 [1.29–1.61]), laparotomy (HR 2.60 [2.04–3.31]), ASA score > 2 (HR 1.70 [1.33–2.16]), smoking (HR 1.64 [1.21–2.21]), antecedent of cancer (HR 1.48 [1.15–1.92]), atrial fibrillation (HR 2.13 [1.54–2.94]), deep vein thrombosis/pulmonary embolism (HR 1.58 [1.09–2.29]), and previous abdominal surgery (HR 0.76 [0.59–0.98]) were confounding factors of death at 3 years. Analysis of the disease location did not show a difference in survival. Due to the rejection of the proportional hazard assumptions for age and laparotomy parameters, they were not entered in the multivariate model (e-Table 3 in supplement). Analysis of 3-year survival by a multivariate Cox model identified the ERAS protocol as a protective factor with a 30% reduction in the risk of death (HR = 0.70 [0.55–0.90]) compared to the pre-ERAS group, after adjustment for ASA score > 2 (HR = 1.44 [1.11–1.87]), smoking (HR = 1.58 [1.16–2.15]), history of cancer (HR = 1.36 [1.04–1.78]), atrial fibrillation (ACFA) (HR = 1.91 [1.35–2.69]), and abdominal surgery (HR = 0.76 [0.58–0.98]) (Table 4).

Discussion

In this large retrospective study, we compared overall survival at 3 years following two rehabilitation strategies in patients recovering from surgery for colorectal cancer.

Table 3 Complications reported at 90-day whole-study population

	Whole population $n=1001$	ERAS $n=497$	Pre-ERAS $n=504$	*p*-value
Global complication	545 (54.5%)	266 (53.5%)	279 (55.4%)	0.560[a]
Surgical complication	323 (32.3%)	174 (35%)	149 (29.6%)	0.065[a]
Medical complication	305 (30.5%)	162 (32.6%)	143 (28.4%)	0.147[a]
Deep abscess/fistula peritonitis	160 (16%)	75 (15.1%)	85 (16.9%)	0.444[a]
Thromboembolic event	27 (2.7%)	17 (3.4%)	10 (2%)	0.161[a]
Superficial abscess or hematoma	135 (13.5%)	59 (11.9%)	76 (15.1%)	0.137[a]
Pneumonia/respiratory complication	67 (6.7%)	38 (7.8%)	29 (5.8%)	0.228[a]
Urinary tract infection	49 (4.9%)	25 (5%)	24 (4.8%)	0.844[a]
Catheter infection	17 (1.7%)	8 (1.6%)	9 (1.8%)	0.829[a]
Acute urine retention	36 (3.6%)	15 (3%)	21 (4.2%)	0.329[a]
Ileus requiring nasogastric tubes	55 (5.5%)	35 (7%)	20 (4%)	**0.033**[a]
Hemorrhage	44 (4.4%)	25 (5%)	19 (3.8%)	0.331[a]
Transfusion	55 (5.5%)	28 (5.6%)	27 (5.4%)	0.848[a]
Acute renal failure	41 (4.1%)	26 (5.2%)	15 (3%)	0.072[a]
Heart complication	59 (5.9%)	34 (6.8%)	25 (5%)	0.207[a]
Other	151 (15.1%)	84 (16.9%)	67 (13.3%)	0.111[a]
Clavien-Dindo complication				
Grade (1–2)	358 (35.8%)	168 (33.8%)	190 (37.7%)	0.199[a]
Grade (3–4)	148 (14.8%)	82 (16.5%)	66 (13.1%)	0.129[a]
Grade (5)	44 (4.4%)	18 (3.6%)	26 (5.2%)	0.236[a]
Grade (3–4–5)	192 (19.2%)	100 (20.1%)	92 (18.3%)	0.453[a]
Re-intervention	151 (15.1%)	85 (17.1%)	66 (13.1%)	0.074[a]
Surgical re-intervention	111 (11.1%)	62 (12.5%)	49 (9.7%)	0.159[a]
Radiological/endoscopic re-intervention	50 (5%)	30 (6.1%)	20 (4%)	0.129[a]

Frequency (number)

[a]Chi-2 test

[b]Fisher-exact test

Overall survival at 3 years after tumor resection was significantly better in the ERAS than in the pre-ERAS group ($p=0.017$), although patients in the ERAS group had statistically more comorbidities and ASA > 2.

Analysis of 3-year survival by a multivariate Cox model identified receiving the ERAS protocol as a protective factor with a 30% reduction in the risk of death compared to the pre-ERAS group, independently of identified confounding factors. An ASA score > 2, smoking, a history of cancer, and atrial fibrillation ACFA were deleterious risk factors linked to death at 3 years.

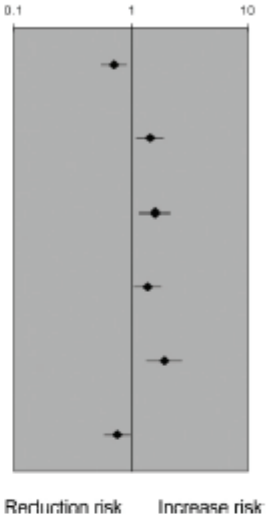
The 3-year overall survival analysis identified the history of abdominal surgery as a protective factor, both in univariate ($p=0.031$) and multivariate (HR = 0.76 [0.58–0.98]; $p=0.032$) analysis. This unintuitive result is explained on the one hand by a heterogeneity of the groups with a higher proportion of patients with a history of abdominal surgery in the ERAS group (51.3 vs 35.2%; $p \leq 0.001$) and on the other hand a death rate at 3 years higher in patients without a history of abdominal surgery (23.3 vs 29.6%; $p=0.028$). The 3-year survival rate in the ERAS group (76.1%) was consistent with those reported by previous studies, with an "ERAS effect" on 3-year and 5-year survival after colorectal resection for cancer. Pisarska et al. [14] reported 3-year survival rates of 76% in non-metastatic patients with ERAS adherence < 80% (group 1) and 88% when adherence was ≥ 80% (group 2). The fact that we included metastatic patients and those operated by laparotomy, known for their poorer prognosis, might explain the lower survival rate compared to Pisarska's group 2. Gustafsson et al. suggested from the results of a Swedish study that high adherence to ERAS may be associated with improved 5-year survival [15].

The 1-year and 3-year survival rates of the pre-ERAS patients in our study were 86.6% and 69.2%, respectively. In a study on the survival of people with colorectal cancer in mainland France between 1989 and 2018, Launoy et al. reported a standardized net survival at 1 year of 84%. The 3-year survival rate varied between 71 and 63% between the ages of 50 and 80 [16]. Thus, our results are comparable to those in the literature.

The total length of hospital stay was significantly shorter in the ERAS group (median 10 days [7–19] for ERAS vs 15

Table 4 Multivariate analysis: risk factors for death at 3 years

Risk factor	Non adjusted hazard ratio (95% CI) *p* value	Adjusted hazard ratio (95% CI) *p* value	Risk factors for death at 3 years adjusted forest plot
Group: ERAS	0.745 (0.586–0.949) p=0.017[a]	0.702 (0.546–0.903) p=0.006[b]	
ASA > 2	1.695 (1.331–2.159) p≤0.001[a]	1.440 (1.110–1.867) p=0.006[b]	
Smoking	1.638 (1.213–2.212) p=0.001[a]	1.581 (1.161–2.153) p=0.004[b]	
History of cancer	1.484 (1.147–1.920) p=0.003[a]	1.363 (1.042–1.782) p=0.024[b]	
Atrial fibrillation	2.128 (1.540–2.941) p=0.001[a]	1.906 (1.349–2.694) p≤0.001[b]	
Abdominal Surgery	0.761 (0.594–0.975) p=0.031[a]	0.755 (0.583–0.976) p=0.032[b]	
Deep vein thrombosis/ pulmonary embolism	1.578 (1.085–2.294) p=0.017[a]	NS[b]	



Hazard ratio (95% confidence Interval)

[a]Univariate Cox analysis

[b]Multivariate Cox analysis

[10–23]; $p = \leq 0.001$) with the median length of stay being reduced by approximately 33% (difference 5 days). However, our lengths of stay were longer than those reported in the literature [17–19]. This could be explained by the fact that in France, patients prefer to stay longer in hospital because they do not pay for hospitalization and examinations, as well as to the notorious lack of post-operative follow-up care structures in our region (with only 3 centers, the city of Grenoble is ranked 30th out of 33 in France) as alternatives to returning home [20].

The 90-day readmission rate was significantly different between the groups, favoring ERAS group, and lower than those reported by Lui et al. [18].

For the whole study population, the rate of complications at 90 days was 54.5%, with a mortality rate of 4.4%. Complications and deaths at 90 days were similar in the ERAS and pre-ERAS groups (53.5 vs 55.4%; $p = 0.560$; and 3.6 vs 5.2%; $p = 0.236$), respectively.

The higher rate of NGT ileus abnormality in the ERAS group could be explained by missing data in the pre-ERAS group, since data for this group was retrieved retrospectively from paper medical files, whereas for the ERAS group, data was more often in electronic files and recorded for prospective studies. Possibly due to this bias, the NGT ileus rate in the two groups in our study remains lower than that usually reported in the literature [21]. A potential explanation for the high complication rate in our study compared to that reported in the literature [17, 22, 23] was that we collected and analyzed major and also minor complications (35.8% were classified as Clavien-Dindo 1–2).

The rate of severe complications (Clavien-Dindo ≥ 3) at 90 days was similar between the two groups. The results of our study patients with conventional rehabilitation (pre-ERAS) are comparable to those reported in a large study of 4875 patients, which reported a major complication rate of 17% at D30 after right or left colectomy [24]. Conversely, the number of severe complications in our ERAS group appears unexpectedly high.

The analysis of the occurrence of severe complications during the first 90 days by the Kaplan Meier method did not show any difference between the ERAS and pre-ERAS patients (e-Fig. 2 in supplement).

This study has some limitations: first, it was a retrospective, single-center cohort. Second, a long recruitment period.

Conclusion

The implementation of the ERAS protocol in our department has been associated with the improvement in 3-year survival, the reduction of the length of hospitalization, and

the rate of readmission. ERAS is also associated with better survival at 3 years, independently of other commonly considered parameters. An ASA score > 2, smoking, a history of cancer, and atrial fibrillation are deleterious risk factors linked to earlier mortality. A 5-year overall survival study is scheduled for early 2023.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00384-022-04155-1.

Declarations

Ethics approval Study ethics approval was obtained on 25 August 2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891) and was registered in the internal register of the Grenoble Alpes University Hospital of studies respecting the reference methodology MR004 of the French National Commission for Informatics and Freedoms (CNIL).

Informed consent Patients were informed that their anonymized data might in the future be the subject of clinical research and could oppose this by informing the doctor.

Patient consent for publication Not required.

Competing interests The authors declare no competing interests.

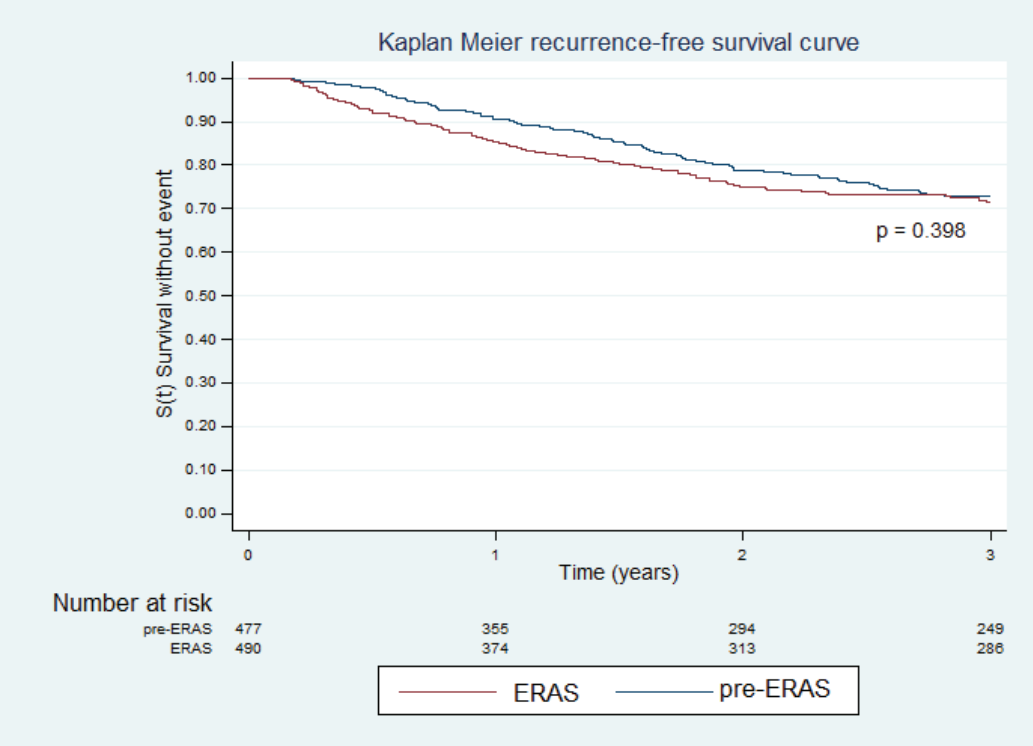
References

1. World Health Organization (WHO) fact sheet - Cancer. Accessed 16 Jul 2021. https://www.who.int/fr/news-room/fact-sheets/detail/cancer
2. Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD (2012) Standards practice task force of the American society of colon and rectal surgeons. Practice parameters for the management of colon cancer. Dis Colon Rectum 55(8):831–843
3. Monson JRT, Weiser MR, Buie WD et al (2013) Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 56(5):535–550
4. Schilling PL, Dimick JB, Birkmeyer JD (2008) Prioritizing quality improvement in general surgery. J Am Coll Surg 207(5):698–704
5. Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH (2015) Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann Surg 261(3):497–505
6. Møiniche S, Bülow S, Hesselfeldt P, Hestbaek A, Kehlet H (1995) Convalescence and hospital stay after colonic surgery with balanced analgesia, early oral feeding, and enforced mobilisation. Eur J Surg 161(4):283–288
7. Kehlet H (2008) Fast-track colorectal surgery. Lancet 371(9615):791–793
8. Kehlet H, Wilmore DW (2008) Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 248(2):189–198
9. Lassen K, Soop M, Nygren J et al (2009) Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 144(10):961–969
10. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN (2010) The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 29(4):434–440
11. Faucheron JL (2013) Laparoscopy in combination with fast-track management is probably the best perioperative strategy in patients undergoing colonic resection for cancer. Ann Surg 257(4):e5
12. Alfonsi P, Slim K, Chauvin M et al (2014) Guidelines for enhanced recovery after elective colorectal surgery. Ann Fr Anesth Reanim 33(5):370–384
13. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213
14. Pisarska M, Torbicz G, Gajewska N et al (2019) Compliance with the ERAS protocol and 3-year survival after laparoscopic surgery for non-metastatic colorectal cancer. World J Surg 43(10):2552–2560
15. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O (2016) Adherence to the ERAS protocol is associated with 5-year survival after colorectal cancer surgery: a retrospective cohort study. World J Surg 40(7):1741–1747
16. French Public Health Authority (Santé Publique France, SFP]). Survival of people with cancer in metropolitan France 1989–2018 - Colon and rectum. (Survie des personnes atteintes de cancer en France métropolitaine 1989–2018 - Côlon et rectum). Accessed 28 Jul 2021. https://www.santepubliquefrance.fr/import/survie-des-personnes-atteintes-de-cancer-en-france-metropolitaine-1989-2018-colon-et-rectum
17. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R et al (2019) Association between use of enhanced recovery after surgery protocol and postoperative complications in colorectal surgery: the postoperative outcomes within enhanced recovery after surgery protocol (POWER) study. JAMA Surg 154(8):725–736
18. Liu VX, Rosas E, Hwang J et al (2017) Enhanced recovery after surgery program implementation in 2 surgical populations in an integrated health care delivery system. JAMA Surg 152(7):e171032
19. Ahmed Ali U, Dunne T, Gurland B, Vogel JD, Kiran RP (2014) Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation? Am J Surg 208(4):663–669
20. Health and social wellbeing website. Follow-up care/Rehabilitation: 875 establishments - Health and social wellbeing. Health and Social Directory (Soins de suite/Réadaptation : 875 établissements - Sanitaire-social. Annuaire Sanitaire et Social). Accessed 20 Jul 2021. https://www.sanitaire-social.com/annuaire/soins-de-suite-readaptation
21. Grass F, Slieker J, Jurt J et al (2017) Postoperative ileus in an enhanced recovery pathway-a retrospective cohort study. Int J Colorectal Dis 32(5):675–681
22. Schwenk W, Haase O, Neudecker J, Müller JM (2005) Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev (3):CD003145
23. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG (2014) The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg 259(5):916–923
24. Kwaan MR, Al-Refaie WB, Parsons HM, Chow CJ, Rothenberger DA, Habermann EB (2013) Are right-sided colectomy outcomes different from left-sided colectomy outcomes?: study of patients with colon cancer in the ACS NSQIP database. JAMA Surg 148(6):504–510

Online data supplement

Contents

e-Figure1. Kaplan Meier recurrence-free survival curve during 3-year follow-up



e-Table 1 – Length of stay in hospital

	Whole Population n=1001	ERAS n = 497	pre-ERAS n = 504	p-value
Length of stay in hospital	13 [8 ; 21]	10 [7 ; 19]	15 [10 ; 23]	≤0.001(4)

Mean ± standard deviation and Median [25th, 75th percentiles],
Student t-test(3), Mann-Whitney test(4)

e-Table 2 – 90-day readmission rate

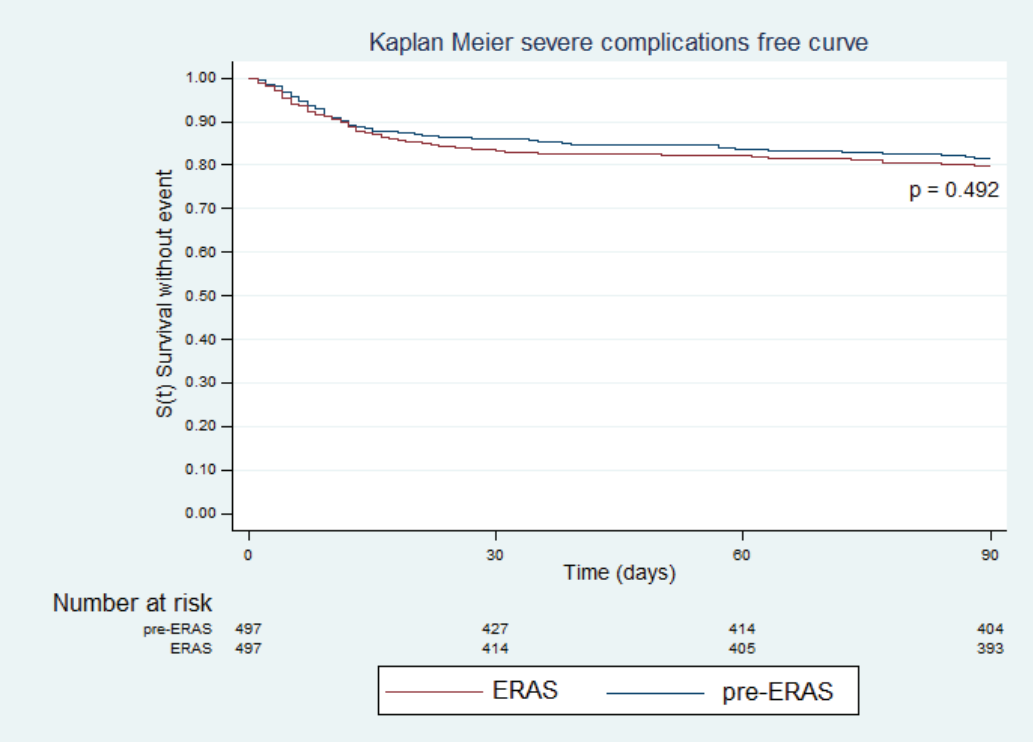
	Whole Population n=997	ERAS n = 493	pre-ERAS n = 504	p-value
90-day readmission rate	17.6% (175)	15% (74) [12%-18.5%]	20% (101) [16.6%-23.8%]	0.037(1)

Frequency (Number) [95%CI], Chi-2 test (1), Fisher-exact test (2)

eTable 3. Risk factors for death at 3 years – univariate analysis

Risk Factor	HR [95 % CI]	p value
ERAS group	0.745 [0.586-0.949]	**p=0.017**[7]
Sex, Male	1.156 [0.898-1.489]	p=0.261[7]
Age, by 10 year bands	1.441 [1.292-1.607]	**p≤0.001** [7]
ASA > 2	1.695 [1.331-2.159]	**p≤0.001**[7]
Laparotomy	2.596 [2.036-3.309]	**p≤0.001**[7]
Neo-Adjuvant Radiotherapy	0.935 [0.680-1.286]	p=0.680[7]
Smoking	1.638 [1.213-2.212]	**p=0.001**[7]
History of cancer	1.484 [1.147-1.920]	**p=0.003**[7]
Number of lymph nodes removed	1.000 [0.984-1.016]	p=0.995[7]
Obesity (BMI > 30)	0.854 [0.570-1.281]	p=0.446[7]
Underweight BMI < 18.5	1.581 [0.962-2.598]	p=0.071[7]
Dyslipidemia	1.041 [0.772-1.403]	p=0.793[7]
Hypertension	1.106 [0.869-1.407]	p=0.414[7]
Atrial fibrillation	2.128 [1.540-2.941]	**p≤0.001**[7]
Deep vein Thrombosis/pulmonary embolism	1.578 [1.085-2.294]	**p=0.017**[7]
Abdominal Surgery	0.761 [0.594-0.975]	**p=0.031**[7]
Colon surgery	0.952 [0.745-1.216]	p=0.694 [7]

eFigure 2. Kaplan Meier Severe complications (Clavien-Dindo 3, 4 and 5) and free survival curve



2. Association entre la réhabilitation améliorée, les facteurs de risque et la survie à 3 ans après chirurgie colorectale pour cancer chez les personnes âgées

Notre première étude a montré que la mise en œuvre du protocole RAC dans notre service est associée à une amélioration de la survie à 3 ans et une réduction à la fois de la durée d'hospitalisation et du taux de réadmission. Elle a également montré un lien entre les facteurs de risque (score ASA > 2, tabagisme, antécédents de cancer et de fibrillation auriculaire) et la mortalité précoce. Cependant, il existe peu de données concernant l'impact de la RAC sur la survie à 3 ans et plus chez les patients âgés, en particulier pour les patients de 75 ans et plus, ces derniers ayant souvent été exclus des essais thérapeutiques[52].

L'objectif principal de cette étude était d'évaluer le lien entre la RAC, les facteurs de risque et la survie globale à 3 ans après chirurgie colorectale pour cancer spécifiquement chez la population âgée de 65 ans et plus.

RESUME

Introduction : Alors que l'espérance de vie augmente actuellement, de plus en plus de patients âgés et fragiles ont besoin d'une résection colorectale pour un cancer. Nous avons cherché à évaluer le lien entre la mise en place du protocole RAC et les facteurs de risques sur la survie globale à 3 ans, chez les patients de 65 ans et plus.

Méthode : Entre 2005 et 2017, tous les patients consécutifs subissant une résection colorectale pour cancer au CHU Grenoble-alpes ont été inclus. La survie globale à 3 ans a été comparée pour les patients traités selon les recommandations RAC par rapport au traitement conventionnel (pré-RAC).

Résultats : 661 patients ont été inclus (RAC, n = 325 ; pré-RAC, n = 336). Le taux de survie globale à 3 ans était significativement meilleur, quel que soit l'âge pour les patients RAC vs pré-RAC (73,1 % vs 64,4 % ; p = 0,016). Avec des taux de SG de 83,2 % vs 73,8 %, 65,4 % vs 62,8 % et 59,6 % vs 40 % pour les tranches d'âge 65-74, 75-84 et ≥ 85 ans, respectivement. L'analyse de la survie à 3 ans par un modèle de Cox multivarié, a identifié le groupe RAC comme un facteur protecteur avec une réduction du risque de décès de 30 % (HR = 0,70 [0,50—0,94], p = 0017), indépendamment des autres facteurs de risque identifiés : tranche d'âge, score ASA > 2, tabagisme, fibrillation auriculaire et chirurgie abdominale. Ce résultat est confirmé par une analyse du score de propension (HR = 0,67 [0,47-0,97] ; p = 0,032).

Conclusion : Nous avons montré que la mise en œuvre du protocole RAC dans notre service est associée à une meilleure survie à 3 ans chez les patients subissant une résection colorectale pour cancer, indépendamment des facteurs de risque. La tranche d'âge, un score ASA > 2, le tabagisme et la fibrillation auriculaire sont des facteurs de risque délétères liés à une mortalité précoce. Les patients âgés de 65 ans et plus bénéficient donc autant de la RAC que la population générale. Ce programme est efficace et doit être proposé pour tous les patients subissant une chirurgie colorectale, y compris ceux âgés de 65 ans et plus.

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-022-02270-1

ORIGINAL ARTICLE

Association between Enhanced Recovery After Surgery (ERAS) protocol, risk factors and 3-year survival after colorectal surgery for cancer in the elderly

Fatah Tidadini[1,2] · Bertrand Trilling[1,3] · Jean-Louis Quesada[4] · Alison Foote[1] · Pierre-Yves Sage[1] · Aline Bonne[1] · Catherine Arvieux[1,2] · Jean-Luc Faucheron[1,3]

Received: 20 July 2022 / Accepted: 26 September 2022

Abstract

Introduction As life expectancy is currently growing, more elderly and fragile patients need colorectal resection for cancer. We sought to assess the link between enhanced rehabilitation after surgery (ERAS), risk factors and overall survival at 3 years, in patients aged 65 and over.

Methods Between 2005 and 2017, all patients undergoing colorectal resection for cancer were included. Overall survival at 3 years was compared for patients treated in following ERAS guidelines compared to conventional treatment (pre-ERAS).

Results 661 patients were included (ERAS, $n=325$; pre-ERAS, $n=336$). The 3-year overall survival rate was significantly better regardless of age for ERAS vs pre-ERAS patients (73.1% vs 64.4%; $p=0.016$). With overall survival rates of 83.2% vs 73.8%, 65.4% vs 62.8% and 59.6% vs 40% for the age bands 65–74, 75–84 and ≥ 85 years. The analysis of survival at 3 years by a multivariate Cox model identified ERAS as a protective factor with a reduction in the risk of death of 30% (HR = 0.70 [0.50—0.94], $p=0017$) independently of other identified risk factors: age bands, ASA score > 2, smoking, atrial fibrillation and abdominal surgery. This result is confirmed by an analysis of the propensity score (HR = 0.67 [0.47–0.97], $p=0.032$).

Conclusions Our study shows that ERAS is associated with better 3-year survival in patients undergoing colorectal resection for cancer, independent of risk factors. The practice of ERAS is effective and should be offered to patients aged 65 and over.

Keywords Colorectal cancer · Colorectal resection · Geriatric, Enhanced Recovery after Surgery (ERAS) · Overall survival, risk factors

Introduction

In 2018, one million new cases of colorectal cancer were diagnosed worldwide. With 43,336 new cases and 17,117 associated deaths recorded in France, colorectal cancer is the second leading cause of cancer death and eight out of ten deaths occur in patients aged 65 and over [1]. On January 1, 2019 this age category comprised 13.4 million French inhabitants, i.e. 20% of the population [2]. Curative treatment calls on for radiotherapy and/or chemotherapy and radical excision surgery [3, 4]. However, colorectal surgery exposes patients to frequent postoperative complications [5], especially in the elderly who often have numerous comorbidities and associated risk factors, resulting in prolonged hospital stay and a higher mortality rate. [6–8]

The implementation of the enhanced rehabilitation after surgery (ERAS) protocol [9, 10], a comprehensive management approach (pre, per and postoperative) to colorectal surgery, has made it possible to reduce morbidity and mortality and shorten the length of hospital stay compared to conventional care [11, 12]. In a systematic review of data from 16 published articles on ERAS in the elderly, Bagnall et al. confirmed that the ERAS program can be safely applied to elderly patients to reduce complications and shorten the

✉ Jean-Luc Faucheron
JLFaucheron@chu-grenoble.fr

1 Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, Grenoble, France

2 Lyon Center for Innovation in Cancer, EA 3738, Lyon 1 University, Lyon, France

3 University Grenoble Alpes, UMR 5525, CNRS, TIMC-IMAG, Grenoble, France

4 Clinical Pharmacology Unit, INSERM CIC1406, Grenoble Alpes University Hospital, Grenoble, France

Published online: 28 October 2022

length of hospital stay [13]. However, there is limited data regarding the impact of ERAS on 3-year and longer-term survival in elderly patients, in particular for patients over 74 years of age, the latter having often been excluded from therapeutic trials [31]. In a study published in May 2022 evaluating the effect of the implementation of the ERAS protocol and risk factors on 3-year survival after colorectal surgery for cancer in the general population [14], we showed that the implementation of ERAS is associated with an improvement in 3-year survival, a reduction in both the duration of hospitalization and the readmission rate. We also showed a link between risk factors (American Society of Anesthesiologists (ASA) score > 2, smoking, history of cancer and atrial fibrillation) and early mortality. The main objective of this study was to evaluate the link between ERAS, risk factors and overall survival (OS) at 3-year survival after colorectal cancer surgery specifically in the elderly population.

Methods

In this study we retrospectively included all consecutive patients undergoing colorectal resection for cancer at Grenoble-Alpes University Hospital (France) between January 2005 and December 2017. The hospital is considered a reference center for colorectal surgery by the French-speaking group for improved rehabilitation after surgery (GRACE) and is also a referent center from the research surgical group for rectal cancer (GRECCAR) group. Patients were pre-selected from the national hospital's medical information database (Programme de Médicalisation des Systèmes d'Information—PMSI) and 661 out of 1072 were finally included. The distribution of patients into ERAS and Pre-ERAS groups was calculated using January 1, 2012, the date of the official launch of the ERAS program in the digestive surgery department, as the point date. It had taken eighteen months from the decision to set-up the program, obtain permissions from the hospital management's, draw up protocols and evaluation procedures, and unite and train a multidisciplinary team of surgeons, anesthesiologists, specialized care and theater nurses, stoma therapists, dieticians, hypnotherapists, physiotherapists, clinical research associates, secretaries etc., to officially starting the ERAS program.

According to the Colorectal Cancer Collaborative Group, definition of elderly patients is an age over 65 years and older and patients were classified into 3 bands age: 65–74 years, 75–84 years and ≥ 85 years [15].

After surgery, patients had been followed daily in the digestive surgery department until hospital discharge, then seen in postoperative consultation at 1 month and followed yearly for at least 5 years after the operation. Patients' survival status was determined by consulting medical records as well as by phone calls (to the patient, their family and/or general practitioner).

Patient and disease characteristics and primary and secondary outcomes were compared for patients managed in ERAS mode (according to the recommendations of the working group of the French society of anesthesia and intensive care (SFAR) and the French society for digestive surgery (SFCD)) [16] compared to the group with conventional care (pre-ERAS, i.e. before introduction of the ERAS protocol).

The main outcome was to evaluate the link between ERAS, risk factors and overall survival (OS) at 3-year survival after colorectal cancer surgery specifically in the elderly population. Secondary outcomes were length of hospitalization, 90-day severe complications (Dindo Clavien 3–5) [17], 90-day readmission, and 3-year disease-free survival (DFS).

All procedures performed in this study followed the recommendations of the committee for ethical standards in research and respected the Helsinki declaration. The study was registered in the internal register of the Grenoble Alpes University Hospital clinical research administration of studies respecting the reference methodology MR004 of the French data protection Agency (CNIL). The work is reported according to the STROCSS criteria. [18]

Statistical analysis

Summary descriptive statistics are used for reporting quantitative parameters, using mean and standard deviation after verification of the application conditions or by median and 25th and 75th percentiles, depending on the distribution of the data. For categorical parameters, numbers and percentages are used. Quantitative parameters were compared between groups using Student's *t* test or a Mann–Whitney test when normality was rejected. Qualitative parameters were compared between groups using a Chi-square test or Fisher's exact test as appropriate.

OS was defined as the time between the date of surgery and death due to any cause, within 3 years follow-up. Survival rates were calculated using the Kaplan–Meier method and compared by treatment group using a Log-Rank test or Cox proportional hazard regression for adjusted models, estimating hazard ratios (HRs) and 95% confidence intervals (95% CI). The same methods were used for DFS at 3 years and severe complication free survival at 90 days. The role of confounding factors was explored using univariate Cox proportional hazard models. A multivariate Cox proportional hazard multivariate model, with backward-stepwise selection (and a 20% threshold), was used to evaluate OS at 3 years for each treatment group.

A propensity score analysis was performed to account for differences in baseline characteristics. The propensity score

was performed on 14 parameters: ASA > 2, high rectal tumor location, dyslipidemia, arterial hypertension, cardiopathy, atrial fibrillation, deep vein thrombosis/pulmonary embolism, renal failure, abdominal surgery, surgery performed by a consultant in surgery, conversion, delayed coloanal anastomosis, ileostomy, and the 3 age bands. This analysis was carried out by pairing the subjects one to one and then comparing them using a univariate Cox model (418 patients), then by a Cox model by adjusting for the propensity score (initial population), then by a Cox model adjusted on the quintile of the propensity score (initial population).

A threshold of 5% was used to define the significance of the statistical tests. No adjustment for multiplicity was applied. Statistical analysis was performed using Stata software version 16.0 (STATA, StataCorp, Texas, USA).

Results

Study population characteristics

Among the 1072 patients who underwent colorectal surgery, 661 (61.7%) were eligible for inclusion in the study (ERAS, $n = 325$; pre-ERAS, $n = 336$) (e-Fig. 1). The demographic and medical characteristics of the population are shown in Table 1. The majority of patients were men 417 (63.2%), the median ([25th; 75th] percentiles) age was 75 [70; 81]. Sixty five (10.1%) patients had metastatic disease; 5 (15.2%) were treated with neoadjuvant chemoradiotherapy and 128 (20.6%) with adjuvant chemotherapy.

In the ERAS group, there were more patients with an ASA score > 2 (56.7% vs 44.6%; $p = 0.002$); and more patients with a history of arterial hypertension (60.9% vs 45.8%; $p \leq 0.001$), abdominal surgery (53.5% vs 38.2%; $p \leq 0.001$), dyslipidemia (26.8% vs 20.2%; $p = 0.048$), cardiac arrhythmia due to atrial fibrillation (17.3% vs 11.6%; $p = 0.038$) and deep vein thrombosis or pulmonary embolism (12.6% vs 7.4%; $p = 0.027$), than in the pre-ERAS group. There were also significantly more resections of the right transverse colon (9.2% vs 4.8%; $p = 0.024$), more laparoscopic interventions (78.2% vs 36.6%; $p \leq 0.001$) and conversions (8.7% vs 3.9%; $p = 0.010$), more ileostomy (21.8% vs 11.3%; $p \leq 0.001$). The number of lymph nodes recovered during lymphadenectomy was also significantly higher in the ERAS group (15 [9; 21] vs 13 [9; 19]; $p = 0.014$) (Table 1). Other characteristics and parameters were comparable between the two groups (Table 1).

Main outcome: 3-year OS rate

The 3-year OS rate was significantly better regardless of age for ERAS vs pre-ERAS patients (73.1% vs 64.4%; $p = 0.016$) (Fig. 1A); with respectively 3-years OS rates of 83.2% vs 73.8%, 65.4% vs 62.8%, 59.6% vs 40% for the age bands 65–74, 75–84 and ≥ 85 years (eTable 1 in supplement). OS at 3 years for the whole series of 661 patients depended on patient age with rates of 78.6%, 64% and 49.5 respectively in the 65–74, 75–84 and ≥ 85 years age bands, $p \leq 0.001$.

The 3 years OS result was confirmed by an analysis of the propensity score (HR = 0.67 [0.47–0.97], $p = 0.032$) with subject matching (Fig. 1B), (HR = 0.72 [0.53–0.97], $p = 0.030$) for the analysis adjusted on the propensity score and (HR = 0.72 [0.53–0.98], $p = 0.035$) for the analysis adjusted on the quintile of the propensity score.

Three-year DFS rate

The 3-year DFS rate adjusted on age bands was similar between the ERAS and pre-ERAS groups patients (74.2% vs 73.8%; $p = 0.580$) (Fig. 2); with respectively DFS rates of 71.5% vs 75.5%, 76.5% vs 73.8%, 76.4% vs 67.6% for the three age bands 65–74, 75–84 and ≥ 85 years (eTable 2 in supplement). DFS at 3 years between the age bands was similar among the 3 age bands: 73.5% vs 75.3% vs 73.4%; $p \leq 0.925$.

The 3-years DFS result was confirmed by competing-risk regression models to take into account competitive risk due to death, estimating sub-distribution of hazard ratios (SHRs) and 95% CIs (SHR = 1.22 [0.87–1.71], $p = 0.253$).

Ninety-day survival without severe complications (Dindo ≥ 3)

The 90-days survival without severe complications adjusted on age bands was similar between the ERAS and pre-ERAS groups (78.1% vs 81.8%; $p = 0.210$). Figure 3 with respectively complication-free survival rates of 80.2% vs 81.9%, 74.2% vs 82.4%, 81.2% vs 80% for the age bands 65–74, 75–84 and ≥ 85 years (eTable 3 in supplement). The 90-days survival rate without severe complications was similar among the three age bands: 81% vs 78.5% vs 80.6%; $p = 0.659$.

Univariate and multivariate analyses

Univariate analysis using a Cox model showed that the age bands 65–74 [(HR = 1.881 [1.365–2.592]) and 75–84 [(HR = 3.022 [2.085–4.380]), laparotomy (HR = 2.492 [1.878–3.306]), ASA score > 2 (HR = 1.406 [1.062–1.862]), smoking (HR = 1.774 [1.247–2.526]), malnutrition (BMI < 18.5) (HR = 1.821 [1.030–3.219]), and atrial fibrillation, (HR = 1.870 [1.335–2.620]) were risk factors for death in the 3 years following surgery, whereas previous abdominal surgery (HR = 0.681

Table 1 Demographic and medical characteristics

	Population $n=661$	pre-ERAS $n=336$	ERAS $n=325$	p value
Demographic characteristics				
Age	75 [70; 81] (65–100)	76 [70; 81] (65–100)	75 [70; 82] (65–96)	0.746[d]
Sex				0.282[a]
(Male)	417 (63.2%)	205 (61.2%)	212 (65.2%)	
(Female)	243 (36.8%)	130 (38.8%)	113 (34.8%)	
BMI	24.9 [22.1;28.3] (15–52.5)	24.9 [22.2;28.4] (15.6–41)	24.9 [22;28.1] (15–52.5)	0.403[d]
Obesity (IMC > 30)	81 (14.8%)	35 (14.9%)	46 (14.7%)	0.936[a]
Underweight (IMC < 20)	32 (5.8%)	14 (6%)	18 (5.7%)	0.911[a]
Medical history				
American Society of Anesthesiologists score (ASA)	3 [2; 3] (1–4)	2 [2; 2] (1–4)	3 [2; 3] (1–4)	**≤ 0.001[a]**
ASA > 2	330 (50.5%)	149 (44.6%)	181 (56.7%)	**0.002[a]**
Colon	447 (67.6%)	225 (67%)	222 (68.3%)	0.712[a]
Right colon	249 (37.7%)	130 (38.8%)	119 (36.6%)	0.562[a]
Right transverse colon	46 (7%)	16 (4.8%)	30 (9.2%)	**0.024[a]**
Left transverse colon	36 (5.5%)	17 (5.1%)	19 (5.9%)	0.656[a]
Left colon	95 (14.4%)	45 (13.4%)	50 (15.4%)	0.466[a]
Rectum	214 (32.4%)	111 (33%)	103 (31.7%)	0.712[a]
High rectum	95 (14.4%)	57 (17%)	38 (11.7%)	0.053[a]
Middle rectum	75 (11.4%)	53 (15.8%)	57 (17.5%)	0.543[a]
Lower rectum	75 (11.4%)	38 (11.3%)	37 (11.4%)	0.976[a]
Haemoglobin	114 [101; 128] (0–175)	111 [97; 127] (0–175)	117 [104; 130] (13–164)	**0.003[d]**
Smoker	85 (12.9%)	43 (12.8%)	42 (12.9%)	0.962[a]
COPD / Respiratory pathology	123 (18.6%)	61 (18.2%)	62 (19.1%)	0.761[a]
Dyslipidemia	255 (23.5%)	68 (20.2%)	87 (26.8%)	**0.048[a]**
HTA	325 (53.3%)	154 (45.8%)	198 (60.9%)	**≤ 0.001[a]**
Cardiopathy	203 (30.7%)	112 (33.3%)	91 (28%)	0.137[a]
Stroke / TIA	57 (8.6%)	25 (7.4%)	32 (9.9%)	0.271[a]
Atrial fibrillation	95 (14.4%)	39 (11.6%)	56 (17.3%)	**0.038[a]**
AOMI	38 (5.8%)	18 (5.4%)	20 (6.2%)	0.660[a]
DVT/PE	66 (10%)	25 (7.4%)	41 (12.6%)	**0.027[a]**
Diabetes	134 (20.3%)	66 (19.6%)	68 (20.9%)	0.682[a]
Renal Failure	77 (11.7%)	33 (9.8%)	44 (13.5%)	0.136[a]
Hepatopathy	35 (5.3%)	17 (5.1%)	18 (5.5%)	0.783[a]
Previous abdominal Surgery	302 (45.8%)	128 (38.2%)	174 (53.5%)	**≤ 0.001[a]**
Other Cancer	198 (30.3%)	101 (30.4%)	97 (30.2%)	0.955[a]
Other medical history	427 (65.6%)	218 (66.1%)	209 (65.1%)	0.798[a]
Treatments	–	–	–	–
Anticoagulant	158 (24.4%)	77 (23.2%)	81 (25.6%)	0.484[a]
Antiaggregant	153 (23.6%)	81 (24.4%)	72 (22.7%)	0.613[a]
Surgery by Senior surgeon	438 (66.4%)	233 (69.4%)	205 (63.3%)	0.099[a]
Surgery by Junior surgeon	222 (33.6%)	103 (30.7%)	119 (36.7%)	0.099[a]
Laparoscopy	377 (57%)	123 (36.6%)	254 (78.2%)	**≤ 0.001[a]**
Laparotomy	284 (43%)	213 (63.4%)	71 (21.9%)	**≤ 0.001[a]**
Robot assisted surgery	5 (0.8%)	0 (0%)	5 (1.5%)	**0.028[b]**
Conversion	41 (6.2%)	13 (3.9%)	28 (8.7%)	**0.010[a]**
ACAD	22 (3.4%)	15 (4.5%)	7 (2.2%)	0.101[a]

Table 1 (continued)

	Population $n=661$	pre-ERAS $n=336$	ERAS $n=325$	p value
Ileostomy	108 (16.5%)	38 (11.3%)	70 (21.8%)	**≤ 0.001**[a]
Associated act	122 (19%)	65 (19.5%)	57 (18.4%)	0.728[a]
Precancerous lesion	21 (3.4%)	12 (3.9%)	9 (2.9%)	0.477[a]
pT				0.438[a]
0	36 (5.8%)	20 (6.6%)	16 (5.2%)	
1	46 (7.5%)	17 (5.6%)	29 (9.3%)	
2	88 (14.3%)	46 (15.1%)	42 (13.5%)	
3	319 (51.8%)	160 (52.4%)	159 (51.1%)	
4	127 (20.6%)	62 (20.3%)	65 (20.9%)	
Lesion pN				0.238[b]
0	381 (63.7%)	181 (62.4%)	200 (64.9%)	
1	148 (24.7%)	80 (28.1%)	68 (22.1%)	
2	68 (11.4%)	29 (9.5%)	39 (12.7%)	
3	1 (0.2%)	0 (0%)	1 (0.3%)	
Metastasis	65 (10.7%)	34 (11.4%)	31 (10%)	0.565[1]
Number of positive lymph nodes	0 [0; 1] (0–25)	0 [0; 1] (0–25)	0 [0; 1] (0–22)	0.812[4]
Number of lymph nodes harvested	14 [9; 20] (0–48)	13 [9; 19] (0–40)	15 [9; 21] (0–48)	**0.014**[4]
R1 resection	27 (4.4%)	13 (4.3%)	14 (4.5%)	0.919[1]
R2 resection	6 (1%)	2 (0.7%)	4 (1.3%)	0.686[2]
Adjuvant chemotherapy	128 (20.6%)	71 (23%)	57 (18.2%)	0.136[1]
Neoadjuvant Radiotherapy	95 (15.2%)	46 (14.8%)	49 (15.7%)	0.764[1]
Duration of intervention (minutes)	165 [115; 220] (32–579)	165 [120; 233] (65–579)	165 [115; 220] (32–532)	0.733[4]
Operating room occupation time (minutes)	240 [200; 330] (112–640) $n=159$	215 [172; 270] (112–535) $n=42$	256 [205; 347] (120–640) $n=117$	**0.005**[4]

Mean ± standard deviation and Median [25th, 75th percentiles], frequency (Number), (Min; Max)

[a]Chi-2 test

[b]Fisher-exact test

[c]Student t test

[d]Mann-Whitney test

[0.512–0.905]) was a protective factor (eTable 4 in supplement).

Analysis of 3-year survival using a multivariate Cox model identified ERAS as a protective factor with a 30% reduction in the risk of death (HR = 0.70 [0.50—0.94], $p=0017$) compared to pre-ERAS, after adjustment on the following confounding factors: age band 75–84 (HR = 1.689 [1.219–2.341]) and age ≥ 85 (HR = 2.857 [1.964–4.156]), smoking (HR = 1.753 [1.220–2.519]), atrial fibrillation (HR = 1.757 [1.234–2.502]), abdominal surgery (HR = 0.736 [0.548–0.988]), as well as ASA score > 2 (HR = 1.230 [0.914–1.656]) (Table 2).

Length of hospitalization stay

The length of hospitalization stay of ERAS patients was shorter compared to pre-ERAS patients (median 11 [8–21] vs 15 days [11–25]; $p \leq 0.001$), (eTable 5 in supplement).

Ninety-day rehospitalization rate

The 90-day readmission rate was significantly different between the ERAS and pre-ERAS groups with 13.3% [9.8–17.5] vs 19.1% [15–23.7]; $p=0.046$ (eTable 6 in supplement) and the rates remained different after adjusting for age bands ($p=0.0370$).

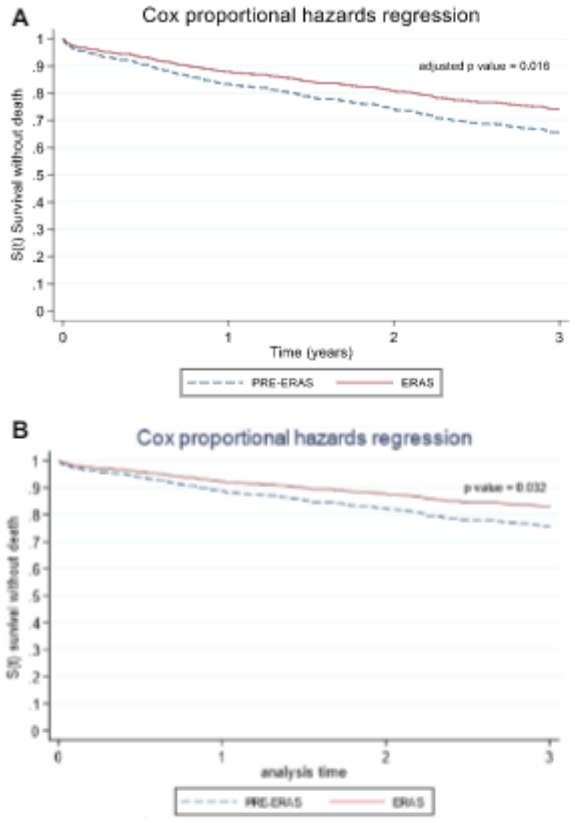


Fig. 1 **A** Cox proportional hazards regression, OS at 3 years between ERAS and pre-ERAS groups adjusted on age groups. **B** Cox proportional hazards regression, OS at 3 years between ERAS and pre-ERAS groups, propensity score analysis

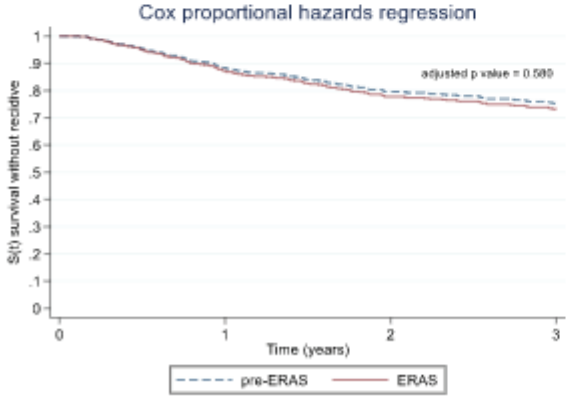


Fig. 2 Cox proportional hazards regression, DFS at 3 years follow-up between ERAS and Pre-ERAS groups adjusted on age bands

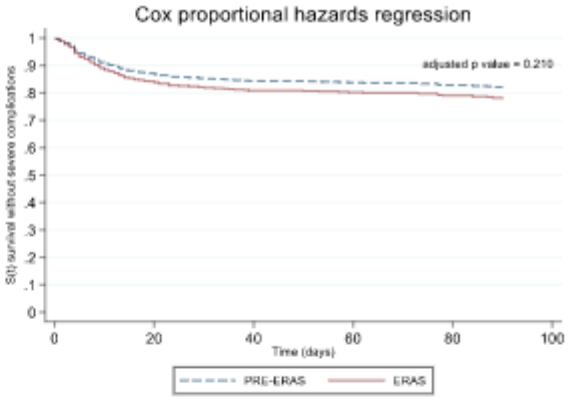


Fig. 3 Cox proportional hazards regression, severe complication-free survival at 90 days follow-up between ERAS and Pre-ERAS groups adjusted on age bands

Discussion

In our cohort, although patients in the ERAS group had statistically more comorbidities and risk factors, the OS rate at 3 years was significantly better regardless of age band compared to the pre-ERAS group ($p = 0.016$), with a difference of 8.7%.

Our study also showed that the OS rate at 3 years depends on the patient's age ($p \leq 0.001$). Joris et al. also reported that ERAS is not only feasible in the elderly, but elderly patients benefit from this program after colorectal surgery as much as younger patients do [19]. In the literature, data regarding the rate of OS at 3 years in elderly patients managed in ERAS mode is unavailable, the latter having often been excluded from clinical trials in colorectal surgery. In a recently published study evaluating the effect of ERAS protocol implementation and risk factors on 3-year survival after colorectal cancer surgery in the general population, we reported OS rates at 1, 2, and 3 years in ERAS patients of 89.7%, 81.5%, and 76.1%, respectively. [14] The OS rates at 1, 2 and 3 years of elderly patients receiving ERAS in our study were 87.6%, 78.2% and 73.1%, respectively, which that is slightly lower than that of the general population. This can be explained by the advanced age of the patients and the number of associated comorbidities, which also play a deleterious role.

Our OS rates at 3 years were 73.8%, 62.8% and 40% for the age bands 65–74, 75–84 and ≥ 85 years, respectively. According to Public Health France, the OS at 3 years of people diagnosed with colorectal cancer between 2010 and 2015 was 73% and 63% for patients aged 70 and 80, respectively. [20] The rate of OS in the 65–74 age band is comparable to that reported for patients aged 70; similarly, the rate of OS

Table 2 Risk factors for death within 3 years—multivariate analysis

Risk factor	Non-adjusted HR [95% CI] *p* value	Adjusted HR [95% CI] *p* value	Risk factors for death within 3 years Adjusted Forest Plot
Group: ERAS	0.712 [0.539–0.942] p=0.017[c]	0.702 [0.525–0.938] p=0.017[f]	
Age band 75–84	1.881 [1.365–2.592] $p \leq 0.001$[c]	1.689 [1.219–2.341] $p=0.002$[f]	
Age ≥ 85	3.022 [2.085–4.380] $p \leq 0.001$[c]	2.857 [1.964–4.156] $p \leq 0.001$[f]	
ASA > 2	1.406 [1.062–1.862] $p=0.017$[c]	1.230 [0.914–1.656] $p=0.172$[f]	
Smoker	1.774 [1.247–2.526] $p \leq 0.001$[c]	1.753 [1.220–2.519] $p=0.002$[f]	
Atrial fibrillation	1.870 [1.335–2.620] $p=0.001$[c]	1.757 [1.234–2.502] $p=0.002$[f]	
Previous Abdominal Surgery	0.681 [0.512–0.905] $p=0.008$[c]	0.736 [0.548–0.988] $p=0.041$[f]	

Hazard ratio [95% confidence interval]

ASA American Society of Anesthesiologists score

[c]Univariate Cox analysis

[f]Multivariate Cox analysis

in our 75–84 age band is similar to that reported for patients aged 80.

The age-adjusted survival without severe complications at 90 days was similar between the ERAS and pre-ERAS groups ($p=0.210$) and among the three patient age bands ($p=0.659$). Similarly, DFS at 3 years was similar in the two groups ($p=0.398$) and among the patient age bands ($p \leq 0.925$). The total length of hospital stay was significantly shorter in the ERAS group ($p \leq 0.001$). The length of stay for patients aged 65 and over is almost the same as that of the general population for the 2 groups (median 10 days [7–19] vs 15 [10–23]) [14]. However, it was longer than those reported in the literature [21–23]. In France, due to lack of social network and primary care, hospitalization may be prolonged due to unavailability of community care. In our public University hospital, some patients may have social problems or degraded living conditions and thus can stay in hospital for days, despite relatively healthy. The 90-day rehospitalization rate was lower for ERAS patients ($p=0.046$). In the literature, Baek et al. reported the rate of emergency room visits or hospital readmissions at 30 days to be 11.7% in patients who underwent laparoscopic colorectal surgery aged 70 and over, a difference of 7.7% compared to patients under 70 [24].

Of course, this study makes a historical comparison between two successive periods and anesthetic, surgical and overall management have made progresses in parallel.

Our study has some limitations. First, it was a monocentric cohort and retrospective, hence there was no randomization. Second, this study makes a historical comparison

between 2 successive phases spanning over a period of 13 years and during these 13 years, new procedures were introduced or improved, in addition to improvements in medical treatment and regimens of neoadjuvant or adjuvant treatments.

In view of the encouraging results of the ERAS protocol, nowadays it might be considered unethical to assign patients to a study arm that does not include ERAS, even for elderly patients.

Conclusion

We have shown that the implementation of ERAS in elderly patients in our department is associated with better 3-year survival after colorectal cancer surgery, independently of risk factors. Age group, smoking, atrial fibrillation and ASA score > 2 are deleterious risk factors linked to early mortality. Patients aged 65 and over therefore benefit from ERAS as much as the general population. This program should be indicated for all patients undergoing colorectal surgery, including those aged 65 and over.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-022-02270-1.

Author contributions Study concept and design: FT, JLF; data acquisition: FT, AB, PYS, BT, CA, JLF; statistical analysis: JLQ; data analysis and interpretation: FT, CA, JLQ, BT, AF, JLF; writing manuscript: FT, AF, JLF. Manuscript review: ALL AUTHORS.

Declarations

Conflict of interest All authors declare no disclosures.

Ethical approval All procedures performed in this study followed the recommendations of the committee for ethical standards in research and respected the Helsinki declaration. The study was registered in the internal register of the Grenoble Alpes University Hospital clinical research administration of studies respecting the reference methodology MR004 of the French data protection Agency (CNIL).

Informed consent For this type of study, formal consent is not required.

References

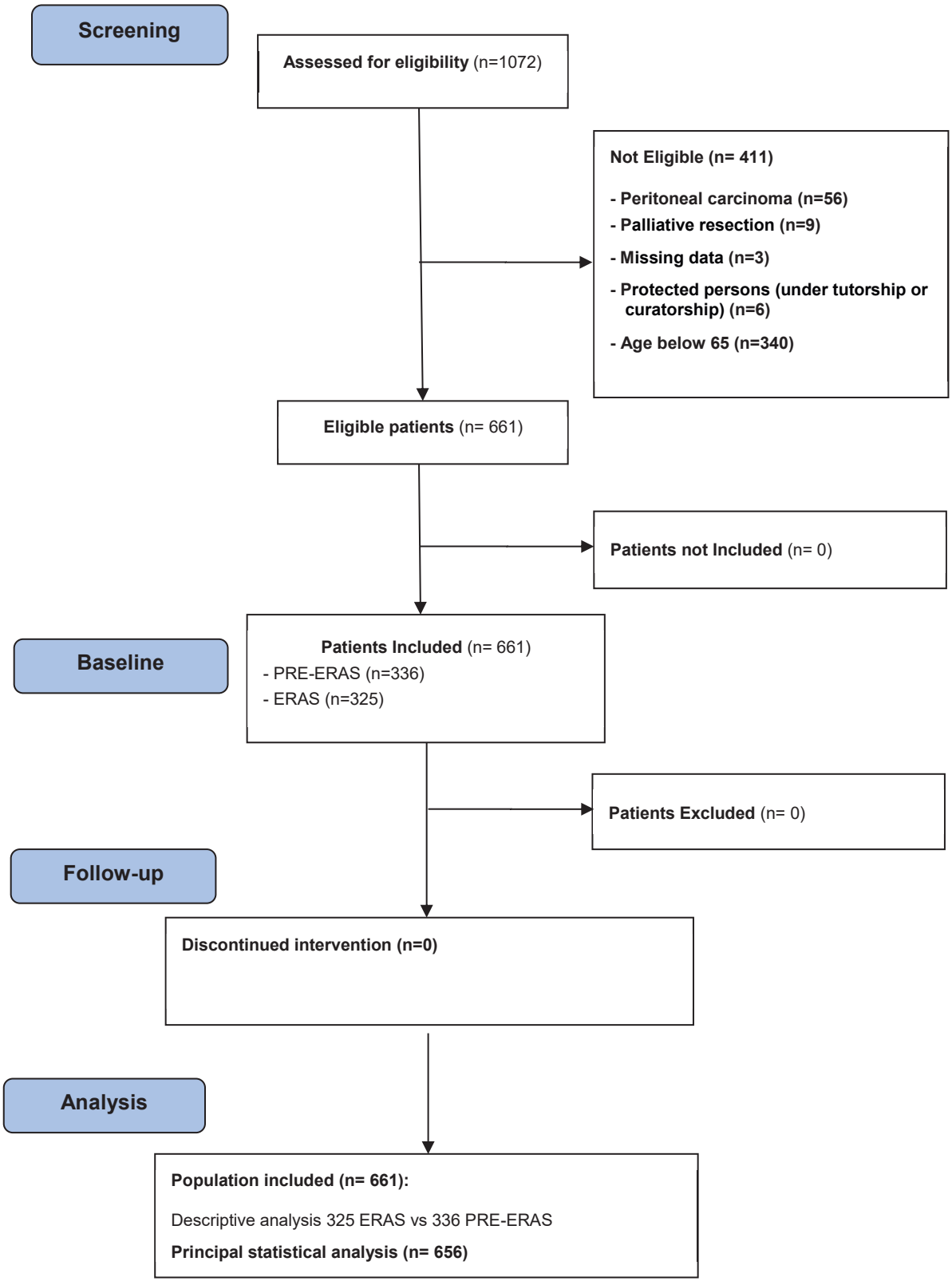
1. Cancer du colon rectum. Accessed June 20, 2022. https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-colon-rectum
2. Seniors—France, portrait socialInsee. Accessed June 23, 2022. https://www.insee.fr/fr/statistiques/4238381?sommaire=4238781
3. Chang GJ, Kaiser AM, Mills S et al (2012) Standards practice task force of the american society of colon and rectal surgeons. Practice parameters for the management of colon cancer. Dis Colon Rectum 55:831–843. https://doi.org/10.1097/DCR.0b013e3182567e13
4. Monson JRT, Weiser MR, Buie WD et al (2013) Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 56:535–550. https://doi.org/10.1097/DCR.0b013e31828cb66c
5. Schilling PL, Dimick JB, Birkmeyer JD (2008) Prioritizing quality improvement in general surgery. J Am Coll Surg 207:698–704. https://doi.org/10.1016/j.jamcollsurg.2008.06.138
6. Marusch F, Koch A, Schmidt U et al (2005) The impact of the risk factor "age" on the early postoperative results of surgery for colorectal carcinoma and its significance for perioperative management. World J Surg 29:1013–1021. https://doi.org/10.1007/s00268-005-7711-6 (Discussion 1021-1022)
7. Tan KY, Kawamura YJ, Tokomitsu A et al (2012) Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. Am J Surg 204:139–143. https://doi.org/10.1016/j.amjsurg.2011.08.012
8. Patients âgés opérés et pris en charge pour un cancer colorectal : étude d'une cohorte monocentrique. Revue Medicale Suisse. Accessed June 23, 2022. https://www.revmed.ch/revue-medicale-suisse/2010/revue-medicale-suisse-250/patients-ages-operes-et-pris-en-charge-pour-un-cancer-colorectal-etude-d-une-cohorte-monocentrique
9. Møiniche S, Bülow S, Hesselfeldt P et al (1995) Convalescence and hospital stay after colonic surgery with balanced analgesia, early oral feeding, and enforced mobilisation. Eur J Surg 161:283–288
10. Kehlet H (2008) Fast-track colorectal surgery. Lancet 371:791–793. https://doi.org/10.1016/S0140-6736(08)60357-8
11. Varadhan KK, Neal KR, Dejong CHC et al (2010) The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. Clin Nutr 29:434–440. https://doi.org/10.1016/j.clnu.2010.01.004
12. Lassen K, Soop M, Nygren J et al (2009) Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 144:961–969. https://doi.org/10.1001/archsurg.2009.170
13. Bagnall NM, Malietzis G, Kennedy RH et al (2014) A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Colorectal Dis 16:947–956. https://doi.org/10.1111/codi.12718
14. Tidadini F, Bonne A, Trilling B et al (2022) Effect of implementation of enhanced recovery after surgery (ERAS) protocol and risk factors on 3-year survival after colorectal surgery for cancer-a retrospective cohort of 1001 patients. Int J Colorectal Dis 37:1151–1159. https://doi.org/10.1007/s00384-022-04155-1
15. Surgery for colorectal cancer in elderly patients (2000) a systematic review Colorectal Cancer Collaborative Group. Lancet 356:968–974
16. Alfonsi P, Slim K, Chauvin M et al (2014) Guidelines for enhanced recovery after elective colorectal surgery. Ann Fr Anesth Reanim 33:370–384. https://doi.org/10.1016/j.annfar.2014.03.007
17. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae
18. Agha R, Abdall-Razak A, Crossley E et al (2019) STROCSS 2019 Guideline: strengthening the reporting of cohort studies in surgery. Int J Surg 72:156–165. https://doi.org/10.1016/j.ijsu.2019.11.002
19. Joris J, Hans G, Coimbra C et al (2020) Elderly patients over 70 years benefit from enhanced recovery programme after colorectal surgery as much as younger patients. J Visc Surg 157:23–31. https://doi.org/10.1016/j.jviscsurg.2019.07.011

20. SPF. Survie des personnes atteintes de cancer en France métropolitaine 1989–2018 - Côlon et rectum. Accessed July 8, 2022. https://www.santepubliquefrance.fr/import/survie-des-personnes-atteintes-de-cancer-en-france-metropolitaine-1989-2018-colon-et-rectum
21. Hendry PO, Hausel J, Nygren J et al (2009) Determinants of outcome after colorectal resection within an enhanced recovery programme. Br J Surg 96:197–205. https://doi.org/10.1002/bjs.6445
22. Rumstadt B, Guenther N, Wendling P et al (2009) Multimodal perioperative rehabilitation for colonic surgery in the elderly. World J Surg 33:1757–1763. https://doi.org/10.1007/s00268-009-0018-2
23. Feroci F, Lenzi E, Baraghini M et al (2013) Fast-track surgery in real life: how patient factors influence outcomes and compliance with an enhanced recovery clinical pathway after colorectal surgery. Surg Laparosc Endosc Percutan Tech 23:259–265. https://doi.org/10.1097/SLE.0b013e31828ba16f
24. Baek SJ, Kim SH, Kim SY et al (2013) The safety of a "fast-track" program after laparoscopic colorectal surgery is comparable in older patients as in younger patients. Surg Endosc 27:1225–1232. https://doi.org/10.1007/s00464-012-2579-7

Online data supplement

Contents

e-Figure 2 – Study Flowchart



e-Table 1 – Overall survival rate at 3 years by treatment groups

	PRE-ERAS n =331	ERAS n =325	p-value	Adjusted p-value
Overall survival rate at 3 years	64.4% [58.9%-69.3%] (116 deaths)	73.1% [67.9%-77.6%] (86 deaths)	0.017[5]	0.016[6]
Age band 65-74	73.8% [66%-80.2%] (39 deaths)	83.2% [76.3%-88.2%] (26 deaths)		
Age band 75-84	62.8% [53.7%-70.6%] (47 deaths)	65.4% [56.1%-73.2%] (41 deaths)		
Age band ≥85	40% [26.5%-53.1%] (30 deaths)	59.6% [44.3%-72%] (19 deaths)		

Frequency [CI 95 %], Log-rank test [5], Cox regression adjusted on age groups [6]

e-Table 2 – Recurrent free survival rate at 3 years

	pre- ERAS n =311	ERAS n =321	p-value	Adjusted p-value
Recidive free survival rate at 3 years	74.2% [68%-79.4%] (60 events)	73.8% [68.3%-78.6%] (74 events)	0.580[5]	0.580[6]
Age band 65-74	75.5% [67%-82.1%] (31 deaths)	71.5% [63.5%-78.1%] (42 deaths)		
Age band 75-84	73.8% [62.9%-82%] (22 deaths)	76.5% [66.7%-83.8%] (23 deaths)		
Age band ≥85	67.6% [43.2%-83.3%] (7 events)	76.4% [59.2%-87%] (9 events)		

Frequency [CI 95 %], Log-rank test [5], Cox regression adjusted on age group [6]

e-Table 3 – Severe complication-free survival rate at 90 days by treatment group

	pre- ERAS n =330	ERAS n =325	p-value	Adjusted p-value
Severe complication-free survival rate at 90 days	81.8% [77.2%-85.6%] (60 events)	78.1% [73.2%-82.2%] (71 events)	0.224[5]	0.210[6]
Age band 65-74	81.9% [74.7%-87.2%] (27 deaths)	80.2% [73.1%-85.7%] (31 deaths)		
Age band 75-84	82.4% [74.7%-88%] (23 deaths)	74.2% [65.3%-81.1%] (31 deaths)		
Age band ≥85	80% [66%-88.7%] (10 deaths)	81.2% [67%-89.7%] (9 deaths)		

Frequency [CI 95 %], Log-rank test [5], Cox regression adjusted on age groups [6]

e-Table 4 – Risk factors for death at 3 years – univariate analysis

Risk Factor	HR [95 % CI]	p value
ERAS	0.712 [0.539-0.942]	**p=0.017**[7]
Age band		
65-74	1.881 [1.365-2.592]	**p≤0.001**[7]
75-84	3.022 [2.085-4.380]	**p≤0.001**[7]
Sex, Male	1.141 [0.852-1.528]	p=0.377[7]
Age, by 10 year band	1.845 [1.530-2.224]	**p≤0.001**[7]
ASA > 2	1.406 [1.062-1.862]	**p=0.017**[7]
Laparotomy	2.492 [1.878-3.306]	**p≤0.001**[7]
Neo-Adjuvant Radiotherapy	1.037 [0.692-1.552]	p=0.861[7]
Smoker	1.774 [1.247-2.526]	**p=0.001**[7]
History of cancer	1.323 [0.990-1.767]	p=0.058[7]
Number of lymph nodes removed	1.004 [0.986-1.023]	p=0.640[7]
Obesity (BMI > 30)	0.783 [0.478-1.282]	p=0.331[7]
BMI < 18.5	1.821 [1.030-3.219]	**p=0.039**[7]
Dyslipidemia	0.842 [0.599-1.183]	p=0.321[7]
Hypertension	0.958 [0.727-1.263]	p=0.761[7]
Atrial fibrillation	1.870 [1.335-2.620]	**p≤0.001**[7]
DVT/PE	1.188 [0.770-1.834]	p=0.436[7]
Abdominal Surgery	0.681 [0.512-0.905]	**p=0.008**[7]
Colon cancer	0.962 [0.718-1.288]	p=0.794[7]

Hazard Ratio [95% Confidence Interval], Univariate Cox analysis [7]

e-Table 5 – Length of stay in hospital by group

	Population n=661	pre-ERAS n = 336	ERAS n = 325	p-value	Adjusted p-value
Length of stay in hospital	13 [9 ; 23]	15 [11 ; 25]	11 [8 ; 21]	≤0.001[4]	

Mean ± standard deviation and Median [25th, 75th percentiles],
Student t-test[3], Mann-Whitney test[4]

e-Table 6 – 90-day readmission rate

	Population n =659	pre-ERAS n =336	ERAS n =323	p-value	Adjusted p-value
90-day readmission rate	107 (16.2%)	64 (19.1%) [15%-23.7%]	43 (13.3%) [9.8%-17.5%]	0.046[1]	0.037[2]

Frequency (Number) [95%CI], Chi-2 test [1], Mantel-Haenszel test [2]

3. Evaluation de la douleur post-opératoire après PIPAC dans le traitement de la carcinose péritonéale

Nous avons montré dans les deux premières études que la mise en œuvre de la RAC est associée à une meilleure survie à 3 ans chez les patients subissant une résection colorectale pour cancer, indépendamment des facteurs de risque, et que la pratique de la RAC est efficace et qu'elle doit être également proposée aux patients âgés de 65 ans et plus.

Nous nous sommes alors intéressés à l'apport de la RAC sur la PIPAC dans le traitement de la carcinose péritonéale et nous avons produit une évaluation de la douleur post-opératoire, incluant les données des 100 premières interventions PIPAC réalisées sur 49 patients, atteints de CP toutes étiologies confondues et traités en mode RAC, selon les recommandations du groupe de travail de la Société française d'anesthésie et de réanimation (SFAR) et de la Société française de chirurgie digestive (SFCD)[53].

RESUME

Introduction : La chimiothérapie intrapéritonéale pulvérisée par aérosols est une nouvelle technique chirurgicale, développée pour le traitement de la carcinose péritonéale initialement non résécable. Notre objectif était d'évaluer la douleur post-opératoire, les facteurs de risques ainsi que la morbi-mortalité après PIPAC.

Méthode : Entre juillet 2016 et septembre 2020, les données de 100 PIPAC à base d'Oxaliplatine (PIPAC Ox) ou de l'association Doxorubicine-Cisplatine (PIPAC C/D) réalisées chez 49 patients atteints de CP, toutes étiologies confondues, ont été analysées.

Résultats : La médiane des procédures PIPAC par patient était de 2 [1-3]. Les patients ont indiqué une douleur maximale à 16h le jour de l'intervention (J0) et à J1 postopératoire à 8h et 16h. Les douleurs post-opératoires modérées à sévères (EVA 4-10) étaient plus fréquentes avec PIPAC Ox qu'avec PIPAC C/D, respectivement 14 (36,8 %) vs 7 (13,5 %) ; p = 0,010. L'hospitalisation était plus longue pour les patients souffrant de douleurs modérées à sévères que pour les autres (médiane 4 jours [3-7] vs 3 jours [2-4], p = 0,004). L'analyse multivariée a identifié l'Oxaliplatine comme un facteur associé à une douleur plus importante (OR [IC 95] : 2,95 [1,10-7,89]). L'administration d'opiacés était similaire après les procédures PIPAC Ox et PIPAC C/D ; p = 0,477.

Conclusion : La PIPAC est tolérée et la douleur est bien contrôlée chez la majorité des patients. La douleur était maximale à 16h à J0 et à 8h et 16h à J1. PIPAC Ox est associé à une douleur plus importante que PIPAC C/D, indépendamment de la prise d'opiacés. La douleur modérée à sévère est associée à des séjours hospitaliers plus longs. Compte tenu de ces résultats cliniques et de la durée d'hospitalisation, la création d'une hospitalisation intermédiaire entre l'ambulatoire et l'hospitalisation conventionnelle (RAC), avec entrée le jour de l'intervention et une sortie à J1 ou J2 si les critères de sortie précoce sont remplis, est peut-être à envisager pour ce traitement.

International Journal of Colorectal Disease
https://doi.org/10.1007/s00384-022-04182-y

CLINICAL STUDY PROTOCOL

Assessment of postoperative pain after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the treatment of peritoneal metastasis

Fatah Tidadini[1,2] · Julio Abba[1] · Jean-Louis Quesada[3] · Laurent Villeneuve[2] · Alison Foote[1] · Magalie Baudrant[1] · Aline Bonne[1] · Olivier Glehen[2] · Bertrand Trilling[1,4] · Jean-Luc Faucheron[1,4] · Catherine Arvieux[1,2]

Accepted: 7 May 2022

Abstract

Purpose Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new surgical technique, for the treatment of initially unresectable peritoneal metastasis (PM). Our objective was to assess postoperative pain and morbidity.

Methods Between July 2016 and September 2020, data from 100 consecutive PIPAC procedures with oxaliplatin (PIPAC Ox) or doxorubicin-cisplatin (PIPAC C/D) in 49 patients with PM (all etiologies) were analyzed. Pain was self-assessed using a visual analog scale (VAS) of 0–10.

Results The median PIPAC procedures per patient were 2 [1–3]. Patients indicated greatest pain at 4 pm on the day of the procedure (D0) and on postoperative D1 at 8 am and 4 pm. Postprocedural moderate-to-severe pain (VAS 4–10) was more frequent with PIPAC Ox than with PIPAC C/D, respectively 14 (36.8%) vs 7 (13.5%); $p=0.010$. Hospitalization was longer for patients with moderate-to-severe pain than for others (median 4 days [3–7] vs 3 days [2–4], $p=0.004$). Multivariate analysis identified oxaliplatin as a factor associated with greater pain (OR [95% CI], 2.95 [1.10–7.89]. Opiate administration was similar after PIPAC Ox and PIPAC C/D procedures, $p=0.477$.

Conclusion PIPAC was well-tolerated, and pain was well-controlled in the majority of patients. Pain was greatest at 4 pm on D0 and 8 am and 4 pm on D1. PIPAC Ox is associated with greater pain than PIPAC C/D, independently of opiate treatment. Moderate-to-severe pain was associated with longer hospital stays.

Keywords Pressurized intraperitoneal aerosol chemotherapy (PIPAC) · Peritoneal carcinoma · Postoperative pain · Treatment of pain

Introduction

Peritoneal metastasis (PM) is the spread of cancer cells in the peritoneum and is a sign of advanced primary or secondary disease, most often associated with a poor prognosis and a median survival of a few months [1]. The standard treatment is systemic chemotherapy. However, the pharmacokinetics of drug diffusion into the peritoneum is poor, with low efficacy compared to other metastatic sites such as the liver or lungs [2]. When the carcinoma is resectable, some selected patients can benefit from locoregional therapeutic approaches involving peritonectomy or hyperthermic intraperitoneal chemotherapy offering a significant benefit in survival [3, 4]. For patients who are initially unresectable, the team of Professor Marc-André Reymond described (in 2012) a new approach of applying chemotherapy agents directly to the peritoneum using a pressurized aerosol, known as pressurized intraperitoneal aerosol chemotherapy (PIPAC) [5]. This technique results in a higher local drug concentration compared to intraperitoneal or intravenous chemotherapy. PIPAC has since been applied to PM of all etiologies [6–13]. Several recent studies have shown that a therapeutic regimen

✉ Catherine Arvieux
carvieux@chu-grenoble.fr

1 Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, Grenoble, France

2 Lyon Center for Innovation in Cancer, EA 3738, Lyon 1 University, Lyon, France

3 Clinical Pharmacology Unit, INSERM CIC 1406, Grenoble Alpes University Hospital, Grenoble, France

4 UMR 5525, CNRS, TIMC-IMAG, University Grenoble Alpes, 38000 Grenoble, France

Published online: 31 May 2022

combining PIPAC and systemic chemotherapy improves the survival of patients with PM, without diminishing quality of life, and can also make the PM resectable and therefore accessible to complete excisional surgery [6, 7, 14–16]. PIPAC treatment, performed under general anesthesia, combines an in-depth exploration of the abdomen, a PCI score assessment, peritoneal biopsies, and cytology if ascites is present, performed before administration of chemotherapy sprayed directly into the abdomen during a laparoscopy. As with any intervention, PIPAC exposes patients to systematic postoperative pain often with a negative impact on recovery and therefore prolongation of their hospital stay [17, 18]. The prevention and treatment of postoperative pain are based on several factors linked to the characteristics of the patient [19–21], perioperative factors, to the treatments and to the organization of postoperative care. To our knowledge, no study evaluating postoperative pain after PIPAC has ever been conducted. Therefore, we conducted a retrospective study including data from the first 100 PIPAC procedures performed on 49 patients with PM of all etiologies and treated in enhanced rehabilitation mode (ERAS), according to the recommendations of the working group of the French Society for Anesthesia and Resuscitation and the French Society of Digestive Surgery [22]. The main objective was to assess postoperative pain after PIPAC and identify its risk factors. Secondary objectives were the rate of morbidity both immediately postoperatively and at D30 and the duration of hospitalization.

Methods

This was a single-center, retrospective study performed at Grenoble Alpes University Hospital (France), an expert center for PIPAC, between July 2016 and September 2020. During this period, 100 consecutive PIPAC procedures with oxaliplatin (PIPAC Ox) or doxorubicin–cisplatin (PIPAC C/D) were performed to treat PM of all etiologies. The study population consisted of adult patients with unresectable PM, in good general condition (WHO < 3), without metastases other than peritoneal, treated with PIPAC administered in alternation with systemic chemotherapy. All patients who received PIPAC treatment in our hospital during the study period were included.

The level of postoperative pain and pain treatments was extracted from medical records. During their hospital stay, patients self-assessed their pain on a visual analog scale (VAS) scale of 0 (no pain) to 10 (worst imaginable pain) 3 times per day, at 8 am, 4 pm, and midnight, and it was recorded by nurses in the patients' medical records. Pain was defined as mild (VAS 1–3), moderate (VAS 4–6), or severe (VAS 7–10). The antalgic treatments were classified into 3 categories according to their potency (level 1, 2, and 3) [23, 24]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other adjuvant treatments for pain relief was recorded.

Intraoperative pain treatment was individualized according to the preoperative anesthesia consultation. In the post-intervention monitoring room, all patients had the same protocol for the use of oxycodone and morphine for moderate-to-severe pain in adults (VAS ≥ 4). The titration of morphine or oxycodone consisted of the successive intravenous injection of small doses, with the aim of gradually reaching the amount corresponding to the patient's analgesia threshold. Titration was done based on pain and sedation scores, as well as respiratory rate, and under continuous monitoring throughout the process. On return to the digestive surgery ward, the administration and dosage of pain treatments were strictly individualized and gradually adapted according to the intensity of the pain and any associated drugs.

All signs of toxicity and postoperative complications occurring during the first 30 postoperative days were extracted from medical records and graded according to the Clavien–Dindo classification [25] with major complications being grades 3 to 5. Complications occurring during the initial hospital stay following a PIPAC procedure were considered to be immediate postoperative morbidities. Complications occurring between hospital discharge and the consultation on D30 were cumulated. Pain on D30 was documented in descriptive or narrative form, such as "patient suffering, painful."

The oncology strategy

PIPAC procedures were performed every 6 to 8 weeks, alternating with systemic chemotherapy and replacing one cycle of intravenous chemotherapy. The type of systemic chemotherapy used between PIPAC procedures had been decided by a multidisciplinary committee. Tumor response was based on surgical assessment using the peritoneal cancer index (PCI) [26], routine intraoperative biopsies, and regular CT scans of the abdomen and chest.

Surgical procedure and PIPAC

All surgeons involved in PIPAC procedures had completed PIPAC training [27]. Procedures were performed in a dedicated operating room with a team of specialist operating room nurses assigned to PIPAC procedures. A safety checklist established before the intervention jointly by the surgeons, the operating room nurses, and the pharmacist was used at the 3 different stages of each procedure.

PIPAC procedures were performed as previously described [5, 28]. Briefly, under general anesthesia, a laparoscopy was performed using an open laparoscopic technique to prevent intestinal wounds, which would

contraindicate the procedure. A 12 mmHg pneumoperitoneum was created, and to ensure the safety of the procedure, the pressure in the pneumoperitoneum was kept constant throughout the procedure. Two laparoscopic balloon trocars (of 11 and 12 mm) were used. A thorough exploration of the abdomen, PCI assessment, peritoneal biopsies, and ascites cytology (in the case of ascites) was performed prior to administration of the chemotherapy aerosol.

The precise drug administration protocol for PIPAC was established in consultation with the specialist hospital pharmacist. For carcinomas of all origin, doxorubicin at a dose of 1.5 mg/m^2 was administered in combination with cisplatin 7.5 mg/m^2 diluted in 40 and 150 mL of 0.9% sodium chloride, respectively. In the case of contraindication, oxaliplatin at a dose of 92 mg/m^2 in a 5% dextrose solution was recommended.

A CE certified CAPNOPEN® nebulizer (Capnomed GmbH, Zimmern o.R., Germany) connected to a high-pressure injector was inserted through the trocars. Nebulization of the drug was initiated remotely after all staff had left the operating room. The treatment was nebulized at 30 mL/min with a maximum pressure of 20 bars over 5 min. After 30 min of application, CO_2 and the remaining toxic aerosols were evacuated through a closed-air evacuation system. The safety checklist was systematically verified and signed by the surgeon in charge and the operating room nurse.

Follow-up

Following each PIPAC procedure, patients were kept under surveillance for at least 24 h and a blood sample was taken on day 1 (D1). Early mobilization and nutrition were encouraged for all patients. All patients had a standard oncology follow-up with regular CT scans, tumor marker tests, and clinical examinations.

Statistical analysis

Continuous data are presented using descriptive statistics (mean ± standard deviation or median [25th; 75th percentiles]). Categorical data are presented using frequencies and percentages. Quantitative parameters were compared between groups using Student's *t* test or a Mann–Whitney test when normality was rejected. Qualitative parameters were compared between groups using a chi-square test or Fisher's exact test, as appropriate.

Univariate and multivariate logistic models, with backward stepwise selection (with a 0.15 threshold), were used to evaluate the association between potential predictors and postoperative pain at 8 am on D1.

A threshold of 5% was used to define the significance of the statistical tests. No adjustment for multiplicity was applied. Statistical analysis was performed using Stata software version 14.2 (STATA, StataCorp, TX, USA).

Results

Between July 2016 and September 2020, 49 consecutive patients with unresectable PM, all etiologies combined (mainly of gastric and colorectal), underwent a total of 100 PIPAC procedures with oxaliplatin or doxorubicin–cisplatin, administered in alternation with systemic chemotherapy. Demographic and medical data and tumor and carcinoma characteristics are presented in Tables 1 and 2. Twenty-seven patients were women (55.1%). At the time of metastasis diagnosis, 79.2% of the PMs were classified as synchronous. The median age was 65 [59; 71] years (median [25–75th percentiles]); the median number of PIPAC procedures was 2 [1; 3]. The median PCI at the start of treatment was 19 [15; 22]. All patients had received at least one line of intravenous chemotherapy (eTable 1 in supplement). The median level of postoperative pain (during their hospital stay) for the study population was 1.5 [0–3].

Postoperative pain

Moderate-to-severe postoperative pain (VAS 4–10) was reported on D0 at 8 am, immediately before the PIPAC procedure in 9.8% of cases. This level of pain was again experienced following 23.3% of procedures at 8 am on D1, following 28.3% on D2, and following 19.2% on D3 (for the morning assessment) (Fig. 1). At about 4 pm on D0 moderate-to-severe pain (VAS 4–10) was felt after 28.3% procedures, after 25% procedures on D1 and after 18.2% procedures on D2 (for the afternoon assessment). Patients indicated greatest pain at 4 pm on the same day as PIPAC (D0) and on postoperative D1 at 8 am and 4 pm, $p < 0.05$, $p < 0.05$, and $p < 0.05$; respectively (Fig. 2a, b and eTable 2 in supplement). There were more procedures with moderate and severe pain (VAS > 3), measured at 8 am D1, with PIPAC Ox compared to PIPAC C/D, 14 (36.8%) vs 7 (13.5%) respectively; $p = 0.010$. The pain seemed to persist until D30 in 24.7% of the cases.

Risk factors for postoperative pain

We looked for risk factors on which it would be interesting to adjust the intensity of postoperative pain. Univariate analyses using a logistic regression model were performed with the following risk factors, age, sex, American Society of Anesthesiologists score (ASA score), WHO performance status (WHO status), PCI score, origin of PM, diabetes, history of other cancers, number of PIPAC procedures, number of lines of systemic chemotherapy, pain treatment (antalgics

Table 1 Demographic characteristics

	Population ($n=49$)
Age	65 [59; 71]
Sex (female)	27 (55.1%)
BMI	22.6 [18.8; 26.3]
WHO performance status	1 [1; 2]
Cancer history	
Previous other type of cancer	11 (22.5%)
Synchronous PM	36 (75%)
Metachronous PM	12 (25%)
Time between metachronous metastasis and primary tumor diagnosis (days)	1498 [740; 3755]
Number of PIPAC procedures	2 [1; 3]
Initial PCI	19 [15; 22]
Type of PIPAC treatment (n = 100)	
Cisplatin/doxorubicin	56 (56%)
Oxaliplatin	44 (44%)
PCI score in patient with multiple PIPAC procedures	
Decreased	20 (45.5%)
Stable	14 (31.8%)
Increased	10 (22.7%)

Frequency (number); mean ± standard deviation or median [25th; 75th percentiles]; and (min–max)

WHO, World Health Organization

1, 2, 3, and adjuvant treatments), oxaliplatin treatment (vs doxorubicin + cisplatin), and the chronology of onset of synchronous PM (vs metachronous), which showed that oxaliplatin treatment (OR [95% CI], 3.62 [1.48–8.85]), use of level 1 antalgics (OR [95% CI], 4.55 [1.72–12]), level 2 antalgics (OR [95% CI], 4.48 [1.80–11.2]), and level 2 or 3 and antalgics (OR [95% CI], 3.65 [1.52–8.73]) were potential predictors of pain at 8 am on postoperative D1 (eTable 3 in supplement). There was no association between postoperative pain and age, sex, BMI, WHO status, diabetes, ASA score, number of PIPAC procedures, chemotherapy lines, synchronous PM, other cancer history, and the origin of the PM. Multivariate analysis identified oxaliplatin treatment compared to doxorubicin + cisplatin treatment as a factor associated with more pain at 8 am on postoperative D1 with an OR [95% CI] of 2.95 [1.10–7.89] (Table 3).

Table 2 Distribution of PIPAC procedures according to the etiology of primary tumor

Origin	Population $n=49$	Procedure PIPAC $n=100$	PCI $n=100$
Stomach	18 (36.7%)	43 (43%)	15 [8; 19]
Colon or rectum	13 (26.5%)	25 (25%)	19 [16; 23]
Ovary	5 (10.2%)	8 (8%)	14 [8; 22]
Peritoneal mesothelium	3 (6.1%)	8 (8%)	24 [21; 26]
Breast	3 (6.1%)	5 (5%)	12 [12; 12]
Appendix	2 (4.1%)	4 (4%)	17 [17; 17.5]
Pancreas	2 (4.1%)	3 (3%)	15 [15; 16]
Digestive without primitive	1 (2%)	2 (2%)	13 [7; 19]
Gall bladder	1 (2%)	1 (1%)	18 [18; 18]
Anal canal	1 (2%)	1 (1%)	35 [35; 35]

Number (frequency); median [25th; 75th percentiles]

Treatment of pain

Level 1, 2, and 3 antalgic administration rates were 66%, 39%, and 12%, respectively. Adjuvant therapy and NSAIDs were administered in 49% and 5% of cases, respectively. The use of level 1 antalgics was more frequent in patients in the PIPAC Ox group ($p=0.001$). The rate of administration of level 2 and 3 antalgics (morphine) was 46% and was similar between the PIPAC Ox and PIPAC C/D groups: 22 (50%) vs 22 (42.9%); $p=0.477$. The combination of opiates (level 2 and 3 antalgics) with adjuvant treatment was used after 30 (30%) procedures: 17 (38.6%) for PIPAC Ox vs 13 (23.2%) after PIPAC C/D; $p=0.095$. Five (5%) patients in the PIPAC Ox group were treated with NSAIDs vs none (0%) in the PIPAC C/D group; $p=0.014$ (eTable 4 in supplement).

Length of hospitalization

For the entire study population, the median hospital stay was 3 days [2; 4.5]. The median length of hospital stay was significantly longer for patients with moderate to severe pain (VAS 4-10 at 8h on D1) compared to patients with slight or mild (VAS 0-3, at the same postoperative time), median 4 [3; 7] vs 3 [2; 4]; $p = 0.004$.

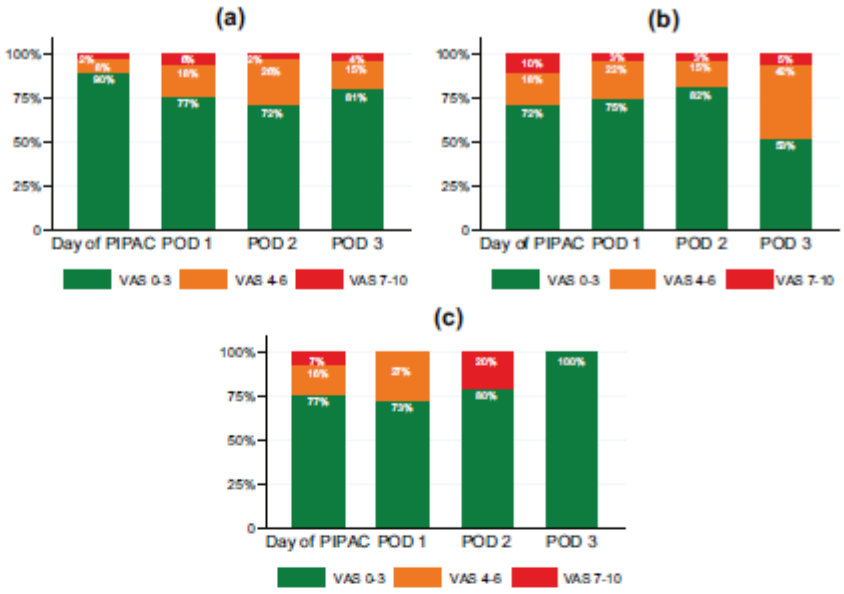


Fig. 1 Distribution of pain score (VAS 0–10) postoperative. **a** 8 am, **b** 4 pm, **c** midnight. VAS, visual analog scale; POD, postoperative day

Immediate postoperative complications

Immediate postoperative complications occurred after 28 (28%) procedures, of which 27 (27%) were classified as benign (Clavien–Dindo 1 and 2). Biological inflammatory syndrome, nausea and vomiting, and fever occurred after 8%, 6%, and 4% of procedures, respectively. One patient (1%) presented a severe complication (Clavien–Dindo 3b), a small perforation of the small bowel requiring return to the operating room for suturing (Table 4).

Postoperative complications at 1 month

Between hospital discharge and D30, postoperative complications had occurred after 34 (35.1%) procedures, of which 32 (32.9%) were classified as benign. Diarrhea, nausea and vomiting, and occlusive episodes occurred after 8.3%, 6.2%, and 5.2% of the procedures, respectively. Thirteen (13.3%) cases of undernutrition and 9 (9.3%) cases of asthenia were recorded. Two patients presented (2%) severe complications (Clavien–Dindo 3–4). One (1%) had removal of an implantable chamber following an infection and 1 (1%) a mini laparotomy for drainage of two fluid collections. Three patients died. The cumulative death rate at D30 was 6.1% (Table 4).

Discussion

In this retrospective study, we assessed postoperative pain following the first 100 PIPAC procedures in our center. Between 8 am on D0 and 4 pm on postoperative D2, the intensity of pain after PIPAC was low or even zero (VAS 0–3) for more than 70% of the procedures. Patients experienced moderate-to-severe pain in less than 28.3% of cases. Due to hospital discharges between D2 and D5, the number of patients was too small to make a meaningful comparison between pain at D0 or D1 and persisting pain several days later. The number of measurements made at midnight from D1 onwards was also very low; thus, the calculated intensity of the pain does not reflect the real pain felt by the patients (Figs. 1c and 2c). Patients indicated greatest pain at 4 pm on D0 and on postoperative D1 at 8 am and 4 pm. Postprocedural moderate-to-severe pain (VAS 4–10) was more frequent with PIPAC Ox than with PIPAC C/D; $p = 0.010$. Taking the time point at which the greatest number of measurements were made, the pain analyses were realized at 8 am on postoperative D1 to optimize the statistical power. Analysis of pain at this time point identified oxaliplatin as a factor associated with more pa both in univariate and multivariate analysis. Surgeons could use this information to better assess which patients may require additional pain control following PIPAC. In the literature, Lindberg et al. found that younger patients experienced more pain after colorectal surgery [29]. Similarly, Thige et al. reported that younger age was related to more postoperative pain in an adult population undergoing a variety of surgical procedures [20]. Rajamäki et al. observed that diabetes mellitus was a risk factor for persistent pain after hip or knee replacement [30]. Caumo et al. and Thige et al. reported that a high ASA score and being female were associated with more postoperative pain after

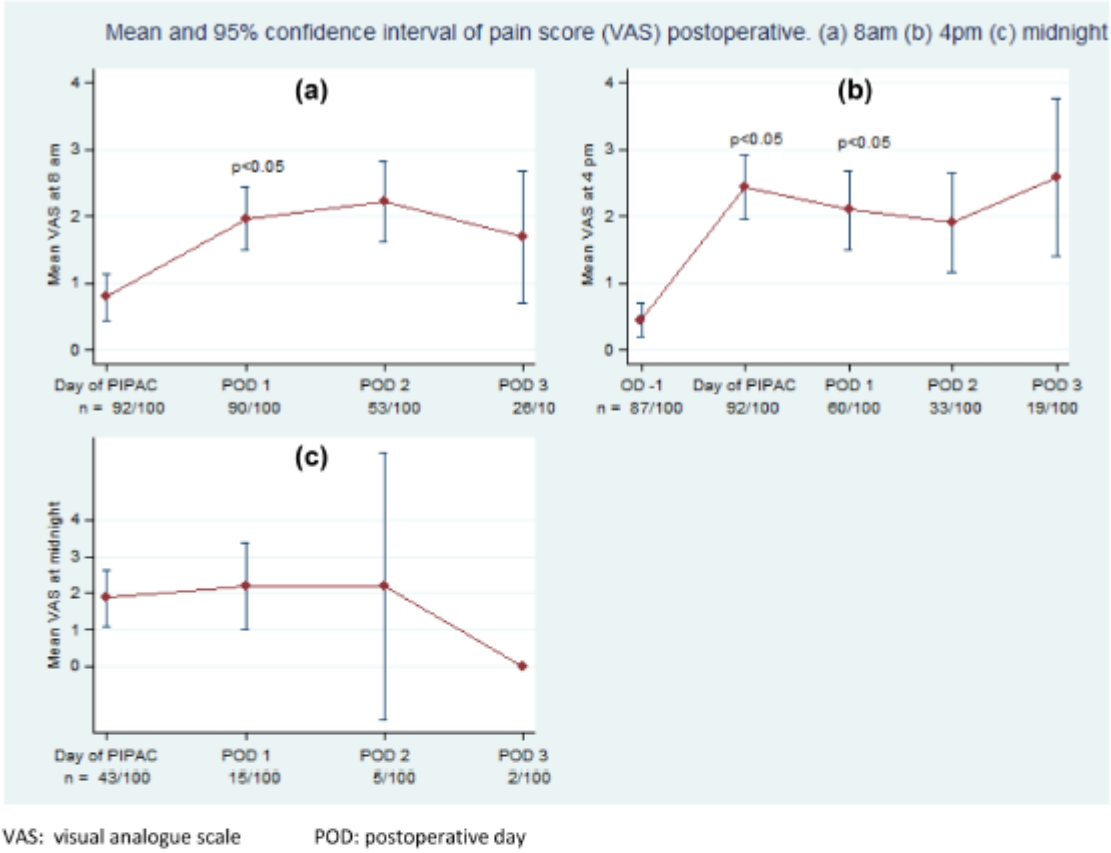


Fig. 2 Mean and 95% confidence interval of pain score (VAS) postoperative. **a** 8 am, **b** 4 pm, **c** midnight. VAS, visual analog scale; POD, postoperative day

other types of surgery [21, 31]. However, our results were not consistent with these reports; age, diabetes, high ASA score, and being female were not significantly related to postoperative pain.

The management and treatment of postoperative pain necessitated the use of opiates (level 2 or 3 antalgics) after 46 (46%) procedures. The ERAS recommendation for postoperative analgesia, especially for colorectal surgery, is

Table 3 Potential risk factors of postoperative pain (measured at 8 am on postoperative D1), multivariate analysis

Risk factor	Non adjusted OR [95% CI] p-value	Adjusted OR [95% CI] p-value	Risk factors of postoperative pain at 8 h on day 1
Type of PIPAC treatment Oxaliplatin	3.62 [1.48 – 8.85] **0.005**[1]	**2.95 [1.10 – 7.89] 0.031**[2]	
Antalgics level 1	4.55 [1.72 – 12] **0.001**[1]	2.28 [0.77 – 6.76] 0.137[2]	
Antalgics level 2 or 3	3.65 [1.52 – 8.73] **0.004**[1]	**2.86 [1.08 – 7.59] 0.035**[2]	Decreased risk Increased risk

Table 4 Postoperative complications

Whole population (100 PIPAC)	Immediate (D0 to D3)	D30 visit
Any complication	28 (28%)	34 (35.1%)
Fistula	1 (1%)	1 (1%)
Wall hematoma	4 (4%)	0 (0%)
Hemorrhage	1 (1%)	0 (0%)
Cardiac complications	2 (2%)	0 (0%)
Parenteral complication	0 (0%)	1 (1%)
Ileus	3 (3%)	0 (0%)
Diarrhea	2 (2%)	8 (8.3%)
Nausea, vomiting	6 (6%)	6 (6.2%)
Asthenia	2 (2%)	9 (9.3%)
Denutrition	0 (0%)	13 (13.3%)
Fever	4 (4%)	1 (1%)
Inflammatory syndrome biological	8 (8%)	1 (1%)
Episode of occlusion	1 (1%)	5 (5.2%)
Other complications	1 (1%)	8 (8.3%)
Mortality	0 (0%)	3 (6.1%)
Causes of mortality		
Major deterioration in general condition	0 (0%)	2 (4%)
Sepsis and occlusive syndrome	0 (0%)	1 (2%)
Clavien–Dindo complication		
Grade (1–2)	27 (27%)	32 (32.9%)
Grade (3–4)	1 (1%)	2 (2.0%)
Grade (5)	0 (0%)	3 (6.1%)

Number (frequency)

multimodal analgesia and only very sparing use of morphine. Thus, all our patients had the same pain management protocol as part of the implementation of the ERAS program in our department. Nevertheless, we recognize that PIPAC treatment can be painful and that the individualized administration of morphine on demand is sometimes necessary for pain control. This flexible mode of management helped control pain in the majority of our patients.

The comparison of the duration of hospitalization between patients with little pain (VAS 0–3) and those with moderate-to-severe intensity pain (VAS 4–10) at 8 am on postoperative D1, the time corresponding to the peak of pain, showed that moderate-to-severe postoperative pain is associated with a prolonged hospital stay $p=0.004$.

During the hospital stay, complications occurred after 28 (28%) procedures. One patient presented with 1 (1%) severe complication (Clavien–Dindo 3b). A thin perforation required return to the operating room for suture. Between hospital discharge and the follow-up visit at D30, complications occurred after 34 (35.1%) procedures. Two patients presented (2%) severe complications (Clavien–Dindo 3–4). Alyami et al. reported major complication rates of 9.7%, and 6.8% patients died within 30 days of the PIPAC procedure [32]. Lurvink et al. reported Common Terminology Criteria for Adverse Events (CTCAE grade 3–4) rates of 0–15% and postoperative mortality rates of 0–2% [33]. The severe morbidity rate (Clavien–Dindo 3–4) in our study was comparable or slightly lower than that in the literature; however, three patients (6.1%) had died by D30 (two for major deteriorations in their general condition and another following sepsis and an occlusive syndrome). In the literature, in a meta-analysis of 106 articles or case reports of PIPAC (including 45 clinical studies with 1810 PIPAC procedures in 838 patients), Alyami et al. reported no mortality in prospective trials, while the mortality in retrospective studies was 2.7% [16].

Given these clinical results, the median length of hospitalization, and economic and psychological considerations, we believe that a shorter length of hospitalization would be possible following a PIPAC procedure, as a compromise between outpatient (or ambulatory) care and conventional practice, with entry on the day of PIPAC and discharge on D1 or D2 if the early discharge criteria are met (clinico-biological evaluation and CHUNG criteria) [34].

Our study has some limitations: firstly, it concerned a retrospective, single-center cohort. Secondly, the patient population was heterogeneous regarding the origin of the PM.

Conclusion

In our experience over 4 years, PIPAC was well-tolerated, and pain was well-controlled for the majority of patients. Pain peaked at the 4 pm assessment on D0 and persisted at the 8 am and 4 pm assessments on D1. PIPAC Ox is associated with greater pain than PIPAC C/D, independently of opiate treatment. Moderate-to-severe pain was associated with longer hospital stays.

Given these clinical results and the length of hospitalization recorded, an intermediate length hospital stay should be considered following PIPAC, as a compromise between outpatient treatment and the 3 to 4 days of hospitalization currently practiced, with entry on the day of the procedure and discharge the following day if the patient's condition meets the criteria for early discharge.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00384-022-04182-y.

Author contribution Study concept and design, Tidadini and Arvieux. Data acquisition, Tidadini, Abba, Trilling, and Arvieux. Quality control of data and algorithms, Tidadini, Abba, Bonne, Baudrant, and Arvieux. Data analysis and interpretation, Tidadini, Abba, Quesada, Glehen, Villeneuve, Faucheron, and Arvieux. Statistical analysis, Quesada.

Manuscript preparation, Tidadini, Faucheron, Foote, and Arvieux. Manuscript editing, Tidadini and Foote. Manuscript review: all authors.

Declarations

Ethics approval All procedures performed in this study were in accordance with the ethical standard research committee and with the Helsinki Declaration. The study was registered in the internal register of the Grenoble Alpes University Hospital of studies respecting the reference methodology MR004 of the French National Commission for Informatics and Freedoms (CNIL).

Consent to participate Patients were informed that their anonymized data might in the future be the subject of clinical research and they could oppose this by informing the doctor.

Competing interests The authors declare no competing interests.

References

1. Dehal A, Smith JJ, Nash GM (2016) Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future. J Gastrointest Oncol 7:143–157. https://doi.org/10.3978/j.issn.2078-6891.2015.112
2. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT et al (2016) Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol 17:1709–1719. https://doi.org/10.1016/S1470-2045(16)30500-9
3. Bonnot P-E, Piessen G, Kepenekian V, Decullier E, Pocard M, Meunier B et al (2019) Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. J Clin Oncol 37:2028–2040. https://doi.org/10.1200/JCO.18.01688
4. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM et al (2018) Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 378:230–240. https://doi.org/10.1056/NEJMoa1708618
5. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA (2012) Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc 26:1849–1855. https://doi.org/10.1007/s00464-012-2148-0
6. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N et al (2016) Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum 1:159–166
7. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond M-A (2016) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. J Gastrointest Surg 20:367–373. https://doi.org/10.1007/s11605-015-2995-9
8. Tempfer CB, Celik I, Solass W, Buerkle B, Pabst UG, Zieren J et al (2014) Activity of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer. Gynecol Oncol 132:307–311. https://doi.org/10.1016/j.ygyno.2013.11.022
9. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J et al (2015) Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol 137:223–228. https://doi.org/10.1016/j.ygyno.2015.02.009
10. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond M-A (2016) Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis 18:364–371. https://doi.org/10.1111/codi.13130
11. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB (2017) Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clin Exp Metastasis 34:309–314. https://doi.org/10.1007/s10585-017-9849-7
12. Khosrawipour T, Khosrawipour V, Giger-Pabst U (2017) Pressurized intra peritoneal aerosol chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS ONE 12:e0186709. https://doi.org/10.1371/journal.pone.0186709
13. Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C (2018) First clinical data of pressurized intraperitoneal aerosol chemotherapy (PIPAC) as salvage therapy for peritoneal metastatic biliary tract cancer. Anticancer Res 38:373–8. https://doi.org/10.21873/anticanres.12232
14. Tidadini F, Abba J, Quesada J-L, Baudrant M, Bonne A, Foote A et al (2021) Effect of pressurized intraperitoneal aerosol chemotherapy on the survival rate of patients with peritoneal carcinomatosis of gastric origin. J Gastrointest Cancer. https://doi.org/10.1007/s12029-021-00698-8
15. Alyami M, Bonnot P-E, Mercier F, Laplace N, Villeneuve L, Passot G et al (2021) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. Eur J Surg Oncol 47:123–127. https://doi.org/10.1016/j.ejso.2020.05.021
16. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N et al (2019) Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol 20:e368–e377. https://doi.org/10.1016/S1470-2045(19)30318-3
17. Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. Lancet 367:1618–1625. https://doi.org/10.1016/S0140-6736(06)68700-X
18. Nimmo SM, Foo ITH, Paterson HM (2017) Enhanced recovery after surgery: pain management. J Surg Oncol 116:583–591. https://doi.org/10.1002/jso.24814
19. Schnabel A, Poepping DM, Gerss J, Zahn PK, Pogatzki-Zahn EM (2012) Sex-related differences of patient-controlled epidural analgesia for postoperative pain. Pain 153:238–244. https://doi.org/10.1016/j.pain.2011.10.022
20. Tighe PJ, Le-Wendling LT, Patel A, Zou B, Fillingim RB (2015) Clinically derived early postoperative pain trajectories differ by age, sex, and type of surgery. Pain 156:609–617. https://doi.org/10.1097/01.j.pain.0000460352.07836.0d
21. Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Adamatti LC et al (2002) Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. Acta Anaesthesiol Scand 46:1265–1271. https://doi.org/10.1034/j.1399-6576.2002.461015.x
22. Alfonsi P, Slim K, Chauvin M, Mariani P, Faucheron J-L, Fletcher D et al (2014) Guidelines for enhanced recovery after elective colorectal surgery. Ann Fr Anesth Reanim 33:370–384. https://doi.org/10.1016/j.annfar.2014.03.007
23. Ventafridda V, Saita L, Ripamonti C, De Conno F (1985) WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React 7:93–96
24. Araujo AM, Gómez M, Pascual J, Castañeda M, Pezonaga L, Borque JL (2004) Treatment of pain in the oncology patient. An Sist Sanit Navar 27(Suppl 3):63–75
25. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications: a new proposal with evaluation in a cohort

of 6336 patients and results of a survey. Ann Surg 240:205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae
26. Jacquet P, Sugarbaker PH (1996) Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 82:359–374. https://doi.org/10.1007/978-1-4613-1247-5_23
27. Alyami M, Sgarbura O, Khomyakov V, Horvath P, Vizzielli G, So J et al (2020) Standardizing training for pressurized intraperitoneal aerosol chemotherapy. Eur J Surg Oncol 46:2270–2275. https://doi.org/10.1016/j.ejso.2020.05.007
28. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C et al (2014) Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol 21:553–559. https://doi.org/10.1245/s10434-013-3213-1
29. Lindberg M, Franklin O, Svensson J, Franklin KA (2020) Postoperative pain after colorectal surgery. Int J Colorectal Dis 35:1265–1272. https://doi.org/10.1007/s00384-020-03580-4
30. Rajamäki TJ, Jämsen E, Puolakka PA, Nevalainen PI, Moilanen T (2015) Diabetes is associated with persistent pain after hip and knee replacement. Acta Orthop 86:586–593. https://doi.org/10.3109/17453674.2015.1044389
31. Tighe PJ, Riley JL, Fillingim RB (2014) Sex differences in the incidence of severe pain events following surgery: a review of 333,000 pain scores. Pain Med 15:1390–1404. https://doi.org/10.1111/pme.12498
32. Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D et al (2017) Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the management of unresectable peritoneal carcinomatosis. Eur J Surg Oncol 43:2178–2183. https://doi.org/10.1016/j.ejso.2017.09.010
33. Lurvink RJ, Van der Speeten K, Rovers KP, de Hingh IH (2021) The emergence of pressurized intraperitoneal aerosol chemotherapy as a palliative treatment option for patients with diffuse peritoneal metastases: a narrative review. J Gastrointest Oncol 12:S259–S270. https://doi.org/10.21037/jgo-20-497
34. Chung F, Chan VW, Ong D (1995) A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 7:500–506. https://doi.org/10.1016/0952-8180(95)00130-a

Online data supplement

Contents

eTable1. Systemic Chemotherapy

Chemotherapy	1st LINE Population n = 49	2nd LINE Population n = 49	3rd LINE Population n = 49
YES (%) **NO (%)**	49 (100%) 0 (0%)	34 (69.4%) 15 (30.6%)	21 (42.9%) 28 (57.1%)
5-FLUOROURACILE-IRINOTECAN-OXALIPLATINE - AFLIBERCEPT	2 (4,1 %)	2 (4,1 %)	-
ALIMTA		1 (2 %)	-
ALIMTA CISPLATINE	1 (2 %)	-	-
ARIMIDEX	-	1 (2 %)	-
AVASTIN		1 (2 %)	1 (2 %)
CAELYX-YONDELIS	-	-	1 (2 %)
CARBOPLATINE - ALIMTA	1 (2 %)	-	-
CARBOPLATIN - PACLITAXEL- AVASTIN		1 (2 %)	-
DOCETAXEL-CISPLATINE - 5 FLUOROURACILE	1 (2 %)	-	-
FOLFIRI	1 (2 %)	2 (4,1 %)	1 (2 %)
FOLFIRI - AVASTIN	-	-	1 (2 %)
FOLFIRI - VECTIBIX	-	-	1 (2 %)
FOLFIRI - ZALTRAP	-	3 (6,1 %)	2 (4,1 %)
FOLFIRINOX	2 (4,1 %)	1 (2 %)	-
FOLFIRINOX - AVASTIN	1 (2 %)	-	-
FOLFOX	22 (44,9 %)	3 (6,1 %)	-
FOLFOX - AVASTIN	4 (8,2 %)	4 (8,2 %)	-
FOLFOX-VECTIBIX	2 (4,1 %)	1 (2 %)	-
GEMCITABINE	-	2 (4,1 %)	-
GEMCITABINE-CISPLATINE	-	2 (2 %)	-
GEMOX	2 (2 %)	-	2 (2 %)
GEMZAR - OXALIPLATINE	-	2 (4,1 %)	-
GEMZAR	-	2 (2 %)	-
GEMZAR-CARBOPLATINE	-	-	2 (2 %)
IPILIMUMAB - TILSOTOLIMOD	-	-	2 (2%)
LONSURF	-	-	2 (2 %)
LV5FU2	2 (4.1%)	2 (2%)	2 (4.1%)
LV5FU2- CISPLATINE	-	2 (2 %)	-
NIVOLIMAB – RELATLIMAB	-	2 (2 %)	-
OXALIPLATINE-5FU	-	2 (2 %)	-
PEMBROLIZUMAB C1	2 (2 %)	-	-
REGORAFENIB - SWITCH LONSURF	-	-	2 (2 %)
STIVARGA	-	-	2 (2 %)
TAXOL	2 (2 %)	2 (2 %)	2 (2 %)
TAXOL - AVASTIN	2 (2 %)	2 (2 %)	-

Chemotherapy	1st LINE Population n = 49	2nd LINE Population n = 49	3rd LINE Population n = 49
TAXOL -CARBOPLATINE	5 (10,2 %)	-	-
TAXOL -CARBOPLATINE- AVASTIN	-	2 (2 %)	-
TAXOTERE	2 (2 %)	-	-
VECTIBIX	-	2 (2 %)	2 (2 %)
XELIRI- AVASTIN	-	-	2 (2 %)
XELODA	-	-	2 (2 %)
XELODA L 2	-	2 (2%)	-

Number (Frequency)

eTable2. Evolution of pain over time

	Pre-operative D-1	Day of PIPAC D0	Post-operative D1	Post-operative D2	Post-operative D3	Post-operative D4	Post-operative D5	p-value
Pain at 8 am		0.8 ± 1.7 (0-7) n=92	2 ± 2.3 §* (0-8) n=90	2.2 ± 2.2 (0-7) n=53	1.7 ± 2.5 (0-10) n=26	1.9 ± 2.6 (0-10) n=15	0.4 ± 1.1 (0-8) n=8	≤0.001(2)
Pain at 4 pm	0.4 ± 1.2 (0-7) n=87	2.4 ± 2.4! * (0-8) n=92	2.1 ± 2.3! * (0-8) n=60	1.9 ± 2.1 (0-8) n=33	2.6 ± 2.4 (0-7) n=19	1.3 ± 1.9 (0-5) n=11	0.7 ± 1.2 (0-2) n=3	≤0.001(2)
Pain at midnight		1.9 ± 2.5 (0-10) n=43	2.2 ± 2.1 (0-6) n=15	2.2 ± 2.9 (0-7) n=5	0 ± 0 n=2	3 n=1	- n=0	0.788(1)

mean ± standard deviation (min-max) or median [25-75th percentiles]
ANOVA (1), Kruskal-Wallis test (2), Wilcoxon signed-rank test (J0 vs JX) (adjusted p value 3)
§ Day of PIPAC vs others, ! OD-1 vs others, * **p≤0.05** (3)

eTable3. Potential risk factors of postoperative pain at 8 am post-operative D1– univariate analysis

Risk factor	Absence of pain n=42	Pain at 8 am D1 n=48	Odds ratio 95 % CI	p-value
Type of PIPAC treatment				
Oxaliplatine	11	27	3.62 [1,48 – 8,85]	0,005 (1)
Cisplatine/Doxorubicine	31	21	-	-
Number of PIPAC procedures				
1 PIPAC	7	12	-	-
2 or 3 PIPAC procedures	35	36	0.60 [0.21 – 1.70]	0.337(1)
Age			0.99 [0.95 – 1.04]	0.733(1)
Sex				
Male	20	21	-	-
Female	22	27	1.17 [0.51 – 2.69]	0.713(1)
ASA Score				
≤2	12	17	-	-
>2	30	31	0.73 [0.30 – 1.78]	0.489(1)
PCI Score			0.98 [0.93 – 1.04]	0.543(1)
Diabetes				
No	38	47	-	-
Yes	4	1	0.20 [0.02 – 1.88]	0.160(1)
Other type of cancer				
No	32	37	-	-
Yes	10	11	0.95 [0.36 – 2.53]	0.920(1)
Origin of the metastasis				
Stomach	19	21	-	-
Colon or rectum	7	15	1.94 [0.65 – 5.77]	0.234(1)
Ovary	5	3	0.54 [0.11 – 2.58]	0.443(1)
Breast	4	1	0.23 [0.02 – 2.21]	0.201(1)
Mesothelium	4	4	0.90 [0.20 – 4.13]	0.897(1)
Pancreas	1	1	0.90 [0.05 – 15.49]	0.945(1)
Appendix	2	1	0.45 [0.04 – 5.40]	0.531(1)
Digestive without primitive	0	-	-	-
Gall bladder	0	1	-	-
Synchronous / Metachrone PM				
Synchronous	28	37	1.85 [0.72 – 4.78]	0.204(1)
Metachronous	14	10	-	-
Chemotherapy line				
1st	15	14	-	-
2nd	9	16	1.90 [0.64 – 5.69]	0.248(1)
3rd	18	18	1.07 [0.40 – 2.85]	0.890(1)
Antalgics level 1				
No	20	8	-	-
Yes	22	40	4.55 [1.72 – 12]	0.002(1)
Antalgics level 2				
No	32	20	-	-
Yes	10	28	4.48 [1.80 – 11.2]	0.001(1)
Antalgics level 2 or 3				
No	28	17	-	-
Yes	14	31	3.65 [1.52 – 8.73]	0.004(1)

Risk factor	Absence of pain n=42	Pain at 8 am D1 n=48	Odds ratio 95 % CI	p-value
Antalgics level 2 or 3 and adjuvant				
No	32	29	-	-
Yes	10	19	2.10 [0.84 – 5.24]	0.113(1)
WHO Performance Status				
0	8	9	-	-
1	22	22	0.89 [0.29 – 2.73]	0.837(1)
2	11	8	0.65 [0.17 – 2.41]	0.516(1)
3	1	6	5.33 [0.52 – 54.3]	0.158(1)
4	0	2	-	-

Odds ratio [95% Confidence Interval], Univariate logistic regression (1), WHO: World Health Organization

eTable4. Treatment of post-operative pain during hospital stay

	Whole Population n =100	Doxorubicin + Cisplatin n =56	Oxaliplatin n =44	p-value
Antalgics level 1	66 (66%)	29 (51.8%)	37 (84.1%)	**0.001**(1)
Antalgics level 2	39 (39%)	20 (35.7%)	19 (43.2%)	0.447(1)
Antalgics level 3	12 (12%)	8 (14.3%)	4 (9.1%)	0.427(1)
Nonsteroidal anti-inflammatory	5 (5%)	0 (0%)	5 (11.4%)	**0.014**(2)
Adjuvant treatment	49 (49%)	23 (41.1%)	26 (59.1%)	0.074(1)
Antalgics level 1 or level 2	71 (71%)	34 (60.7%)	37 (84.1%)	**0.011**(1)
Antalgics level 1 and level 2	34 (34%)	15 (26.8%)	19 (43.2%)	0.086(1)
Antalgics level 2 or level 3	46 (46%)	24 (42.9%)	22 (50%)	0.477(1)
Antalgics level 3 and (level 1 or level 2)	11 (11%)	7 (12.5%)	4 (9.1%)	0.751(2)
Antalgics (level 1 or 2 or 3) and adjuvant treatment	44 (44%)	19 (33.9%)	25 (56.8%)	**0.022**(1)
Antalgics (level 2 or 3) and adjuvant treatment	30 (30%)	23 (23.2%)	17 (38.6%)	0.095(1)

Frequency (Number), Chi-2 test (1), Fisher exact test (2)

III.1.2. Partie 2 : Bénéfices et risques de la PIPAC

4. Résultats oncologiques de la chimiothérapie intrapéritonéale pulvérisée par aérosols dans le traitement de la carcinose péritonéale

Dans cette deuxième partie de notre travail, nous nous sommes intéressés aux bénéfices et risques de la PIPAC dans le traitement de la carcinose péritonéale. Cette chimiothérapie est proposée dans notre hôpital depuis juillet 2016.

Nous avons réalisé une évaluation médicale et économique de ce traitement au cours des cinq premières années de sa mise en œuvre dans notre établissement. Nous avons commencé par l'étude des résultats oncologiques de cette thérapie.

RESUME

Introduction : La chimiothérapie intrapéritonéale pulvérisée par aérosols est une nouvelle technique chirurgicale, pour le traitement de la carcinose péritonéale, initialement non résécable. Notre objectif était d'évaluer les résultats oncologiques de ce traitement.

Méthode : Entre juillet 2016 et septembre 2020, les données de 100 procédures PIPAC à base d'Oxaliplatine ou de l'association Doxorubicine-Cisplatine, chez 49 patients atteints de CP toutes étiologies, ont été analysées. Nous avons étudié l'évolution de l'index de cancer péritonéal (PCI), la chirurgie radicale (R0) et la SG.

Résultats : L'âge médian des patients était de 65 ans [59 ; 71] ans, et 55,1 % étaient des femmes. La médiane des procédures PIPAC par patient était de 2 [1-3], et 28 (57,1 %) ont subi plus d'une procédure PIPAC. Le PCI médian au début du traitement PIPAC était de 19 [15-22]. Le PCI a diminué pour 37 %, est resté stable pour 29,6 % et a augmenté pour 33,4 % des patients. Quatre (8,3 %) ont subi une chirurgie R0 radicale après PIPAC.

Après un suivi médian de 16,1 mois (1,5-90,1), la SG médiane à partir du diagnostic de la CP était de 29,1 mois [14,8-34,3], avec une survie médiane de 11,3 [7,2-34,3] et 29,1 mois [16.1-31] respectivement pour les CP gastrique et colorectale. La SG après la première séance PIPAC était de 11,6 mois [6-17, 3], avec une survie médiane de 6 [2,9-15,5] les CP gastriques et 13,3 mois [5-17, 6] pour l'origine colorectale. La stratification des patients selon le nombre de lignes de chimiothérapie systémique, le nombre de procédures PIPAC et la chronologie d'apparition des PC gastrique et colorectale (métachrone ou synchrone) n'a pas entraîné de différence significative de survie.

Conclusion : La SG était comparable à la littérature. La PIPAC pourrait retarder la progression oncologique et améliorer la survie. Ces résultats encourageants justifient les évaluations en cours et à venir de la PIPAC par des essais prospectifs randomisés.

Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-022-00843-x

ORIGINAL RESEARCH

Oncological Outcomes After Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in the Treatment of Peritoneal Carcinomatosis

Fatah Tidadini[1,2] · Julio Abba[1] · Jean-Louis Quesada[3] · Bertrand Trilling[1,4] · Aline Bonne[1] · Alison Foote[1] · Jean-Luc Faucheron[1,4] · Catherine Arvieux[1,2]

Accepted: 11 June 2022

Abstract

Background Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new surgical technique for the treatment of initially unresectable peritoneal carcinomatosis (PC). Our objective was to assess its oncological outcomes.

Methods Between July 2016 and September 2020, data from 100 PIPAC procedures with oxaliplatin or doxorubicin-cisplatin in 49 patients with PC (all etiologies) were analyzed. We studied the evolution of the peritoneal cancer index (PCI), the need for radical surgery (R0), and overall survival (OS).

Results The patients' median age was 65 (59; 71) years, and 55.1% were women. Median PIPAC procedures per patient were 2 (1–3), and 28 (57.1%) underwent more than one PIPAC procedure. Median PCI at the first PIPAC was 19 (15–22). PCI decreased for 37%, remained stable for 29.6%, and increased for 33.4% patients. Four (8.3%) underwent radical R0 surgery after PIPAC. After a median follow-up of 16.1 months (1.5–90.1), the median overall survival from PC diagnosis was 29.1 months (14.8–34.3), with a median gastric and colorectal PC survival of 11.3 (7.2–34.3) and 29.1 months (16.1–31) respectively. Overall survival after the first PIPAC session was 11.6 months (6–17.3), with median survival after gastric and colorectal PCs being 6 (2.9–15.5) and 13.3 months (5–17.6), respectively. Stratification of patients according to the number of lines of systemic chemotherapy, PIPAC procedures, and the chronology of PC onset did not result in a significant difference in survival.

Conclusion The OS was in line with the literature. PIPAC could delay oncological progression and improve survival. These encouraging results justify the ongoing and future evaluations of PIPAC by prospective randomized trials.

Keywords Pressurized intraperitoneal aerosol chemotherapy (PIPAC) · Peritoneal carcinoma · Overall survival · Oncological outcomes

Introduction

Peritoneal carcinomatosis (PC) is the spread of cancer cells in the peritoneum, and is a sign of advanced primary or secondary cancer, most often associated with a poor prognosis and a median survival of only a few months [1]. The standard treatment is systemic chemotherapy. However, the pharmacokinetics of drug diffusion into the peritoneum is poor, with low efficacy compared to other metastatic sites such as the liver or lungs [2]. When the carcinoma is resectable, suitable patients can benefit from locoregional therapeutic approaches involving peritonectomy or hyperthermic intraperitoneal chemotherapy, offering significant benefits in survival [3, 4]. In 2012, for patients who are initially unresectable, the team of Professor Marc-André Reymond described a new approach applying

✉ Catherine Arvieux
carvieux@chu-grenoble.fr

1 Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, CS 10232, 38043, 38043, CEDEX 09 Grenoble, France

2 Lyon Center for Innovation in Cancer, EA 3738, Lyon 1 University, Lyon, France

3 Clinical Pharmacology Unit, INSERM CIC 1406, Grenoble Alpes University Hospital, Grenoble, France

4 UMR 5525, CNRS, TIMC-IMAG, University Grenoble Alps, Grenoble, France

Published online: 01 July 2022

chemotherapy agents directly to the peritoneum using a pressurized aerosol, known as pressurized intraperitoneal aerosol chemotherapy (PIPAC) [5]. This technique results in a higher local drug concentration compared to intraperitoneal or intravenous chemotherapy. PIPAC has since been applied to PC of all etiologies [6–13]. Several recent studies have shown that a therapeutic regimen combining PIPAC and systemic chemotherapy improves the survival of patients with PC, without diminishing quality of life, and can also render the PC resectable and therefore accessible to complete excisional surgery [6, 7, 14–16]. PIPAC treatment, performed under general anesthesia, combines an in-depth exploration of the abdomen, a PCI score assessment, and peritoneal biopsies (and cytology if ascites is present) performed before administration of chemotherapy sprayed directly into the abdomen during a laparoscopy. PIPAC was introduced in our university hospital in 2016. We now have had sufficient length of follow-up to evaluate not just the short- and medium-term outcomes of PIPAC, but also the longer term outcomes. The outcomes we have investigated are the change in the peritoneal carcinomatosis index (PCI) [17], the opportunity of radical surgery after treatment, and the overall survival (OS) from the diagnosis of CP and from the first PIPAC procedure. We considered the entire population and stratified it according to the origin of the CP, the number of PIPACs, the number of lines of chemotherapy, and the chronology of onset of carcinomatosis (synchronous or metachronous).

Methods

This was a retrospective study performed at Grenoble Alpes University Hospital (France), an expert center for PIPAC, between July 2016 and September 2020. During this period, 100 consecutive PIPAC procedures with oxaliplatin or doxorubicin-cisplatin were performed to treat CP. All patients who received PIPAC treatment in our hospital during the study period and who had been evaluated by an interdisciplinary tumor board were included in this study. The inclusion criteria were as follows: adult with unresectable PC of any etiology, non-eligible for complete cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC); and patients with evolving peritoneal disease after or during systemic chemotherapy, in good general condition (WHO < 3), without metastasis other than peritoneal, and treated with PIPAC administered in alternation with systemic chemotherapy.

Patient vital status was determined from medical records and from phone calls, using September 18, 2020, as the date point. The times were calculated from the dates of diagnosis of carcinomatosis and from the first PIPAC procedure.

The Oncology Strategy

PIPAC procedures were performed every 6 to 8 weeks, alternating with systemic chemotherapy and replacing one cycle of intravenous chemotherapy. The type of systemic chemotherapy used between PIPAC procedures had been decided by a multidisciplinary committee. Response was based on surgical assessment using the PCI, routine intraoperative biopsies, and regular CT scans of the abdomen and chest.

PIPAC Procedure

All surgeons involved in PIPAC procedures had completed PIPAC training [18]. Procedures were performed in a dedicated operating room with a team of specialist operating-room nurses assigned to PIPAC procedures. At the 3 different stages of each procedure, a safety checklist, drawn up before the intervention jointly by the surgeons, the operating-room nurses, and the pharmacist, was completed.

PIPAC procedures were performed as previously described [5, 19]. Briefly, under general anesthesia, a laparoscopy was performed using an open laparoscopic technique to prevent intestinal wounds, which would contraindicate the procedure. A 12 mmHg pneumoperitoneum was created, and to ensure safety, the pressure in the pneumoperitoneum was kept constant throughout the procedure. Two laparoscopic balloon trocars (of 11 and 12 mm) were used. A thorough exploration of the abdomen, PCI assessment, peritoneal biopsies, and ascites cytology (in the case of ascites) were performed prior to administration of the chemotherapy aerosol.

The precise drug administration protocol for PIPAC was established in consultation with the specialist hospital pharmacist. For carcinomas of all origins, doxorubicin at a dose of 1.5 mg/m^2 was administered in combination with cisplatin at 7.5 mg/m^2 diluted in 40 and 150 mL of 0.9% sodium chloride, respectively. In the case of contraindication, oxaliplatin at a dose of 92 mg/m^2 in a 5% dextrose solution was recommended.

A CE certified CAPNOPEN® nebulizer (Reger Medizintechnik GmbH, Villingendorf, Germany) connected to a high-pressure injector was inserted through the trocars. Nebulization of the drug was initiated remotely after all staff had left the operating room. The treatment was nebulized at 30 mL/min with a maximum pressure of 20 bars over 5 min. After 30 min of application, CO_2 and the remaining toxic aerosols were evacuated through a closed-air evacuation system. The safety checklist was systematically completed, and signed by the surgeon in charge and the operating-room nurse.

.....

Follow-up

Following each PIPAC procedure, patients were kept under surveillance for at least 24 h and a blood sample was taken on day 1. Early mobilization and nutrition were encouraged for all patients. All patients had a standard oncology follow-up with regular CT scans, tumor marker tests, and clinical examinations.

Statistical Analysis

Continuous data are presented using descriptive statistics (mean ± standard deviation or median [25th; 75th percentiles]). Categorical data are presented using frequencies and percentages. Quantitative parameters were compared between groups using Student's *t* test or the Mann–Whitney test when normality was rejected. Qualitative parameters were compared between groups using the Chi-square test or Fisher's exact test as appropriate. Changes of one or more points were used to class the PCI score as increasing, decreasing, or stable (if it did not change). Overall survival (OS) was defined as the time from the date of PC diagnosis until the date of death due to any cause or date-of-end of follow-up. Survival rates were calculated using the Kaplan–Meier method. Comparisons of overall survival were analyzed using log-rank tests. A threshold of 5% was used to define the significance of the statistical tests. No adjustment for multiplicity was applied. Statistical analyses were performed using Stata software version 14.2 (STATA, StataCorp, Texas, USA).

Results

Between July 2016 and September 2020, 49 consecutive patients with unresectable PC, all etiologies combined (mainly gastric and colorectal), underwent a total of 100 PIPAC procedures with oxaliplatin or doxorubicin-cisplatin, administered in alternation with systemic chemotherapy. Demographic and medical data, and primary tumor and metastasis characteristics, are presented in Table 1. The median age was 65 (59; 71) years (median (25th–75th percentiles) and 27 patients were women (55.1%). At the time of carcinomatosis diagnosis, 36 (75%) PCs were classified as synchronous. The median number of PIPAC procedures was 2 (1; 3). Nine (18.4%) patients had previously undergone surgery for the primary cancer. All patients had received at least one line of intravenous chemotherapy (Table 2).

PCI in Patients with Multiple PIPAC Procedures

The median initial PCI for the whole study population was 19 (15–22). Among the 28 patients (57.1%) who received more than one PIPAC, PCI decreased for 10 (37%), remained stable for 8 (29.6%), and increased for 9 (33.4%) patients (Fig. 1). One patient could not be taken into account in the evaluation.

Radical Surgery After Treatment

Four patients (8.3%) underwent radical R0 resection with hyperthermic intraperitoneal chemotherapy (HIPEC) after PIPAC, of which 2 (4.1%) had PC of gastric origin, one (2%) with PC of ovarian origin, and one (2%) peritoneal mesothelioma (Table 3).

Overall Survival

The median duration of patient follow-up was 16.1 months (1.5–90.1) (min–max). Two patients were excluded from the survival analysis: one because no carcinomatosis was found during laparoscopy; nevertheless, he had received PIPAC; and the other due to excessive missing data. Thus, the analysis included data from 47 patients. The median OS from the diagnosis of PC was 29.1 months (14.8–34.3), all etiologies combined (Fig. 2A), with a median OS for the 3 main primary tumor origins (gastric, colorectal, and ovarian) of 11.3 (7.2–34.3), 29.1 (16.1–31), and 35.5 (3.2–40.1) months respectively (Fig. 2B). A comparison of patients among those who had one line (49), 2 lines (34), and 3 lines (21) of systemic chemotherapy (Fig. 2C) or among the number of PIPAC procedures (one (19), 2 (13), and 3 or more PIPAC (15) procedures (Fig. 2D)) showed no significant difference in survival (12.8 (6.6–56.1), 24.7 (10.6–90.1), 31 (16.1–51.3), $p=0.215$; and 30.5 (6.6–51.3), 24.7 (7–56.1), 25.6 (11.3–42.6), $p=0.862$), respectively. The comparison of OS according to whether the PC was of gastric or colorectal origin, or was synchronous or metachronous, showed no difference in OS (11.3 (6.6–34.3), 12.8 (6.6–14.8), $p=0.401$; and 30.5 (16.1–51.3), 12.3 (12.3–25.6) months, $p=0.094$) (Fig. 2E and F), respectively.

When taken from the first PIPAC procedure, median OS, all origins combined, was 11.6 (6–17.3) months (Fig. 3A), with a median OS for the 3 main primary tumor origins (gastric, colorectal, and ovarian) of 6 (2.9–15.5), 13.3 (5–17.6), and 13.9 months (1.8–37.8), respectively (Fig. 3B). Stratification of patients according to the number of lines of systemic chemotherapy (1, 2, or 3 lines) (Fig. 3C) and according to the number of PIPAC procedures (1, 2, or 3 or more) (Fig. 3D) did not show any significant difference in survival (6 (2.7–22.6), 13.3 (5.8–40.1), 15.5 (3.7–20.6), $p=0.322$; and 11.6 (2.7–20.6), 6 (3.6–14.4), 15.5 (7–40.1), $p=0.306$), respectively. Comparing OS according to whether patients had synchronous or metachronous PC (gastric or colorectal origins) did not show any difference in OS (6 (2.9–22.6), 3 (0.8–7), $p=0.058$; and 13.3 (5–20.6), 9.8 (9.8–17.3), $p=0.593$) (Figs. 2E and 3F), respectively.

Table 1 Patient characteristics

	Population ($n=49$)
Age	65 (59; 71)
Sex (female)	27 (55.1%)
BMI	22.6 (18.8; 26.3)
ASA score > 2	35 (71.4%)
WHO performance status	1 (1; 2)
Cancer history	
Previous other type of cancer	11 (22.5%)
Surgical treatment of primary tumor before carcinomatosis	9 (18.3%)
Synchronous PC	36 (75%)
Metachronous PC	12 (25%)
Time between primary tumor diagnosis and metachronous carcinomatosis (days)	1498 (740; 3755)
Number of PIPAC procedures	2 (1; 3)
Initial PCI	19 (15; 22)
Origin of PC	
Stomach	18 (36.7%)
Colon or rectum	13 (26.5%)
Other	18 (36.7%)
Type of PIPAC treatment (n = 100)	
Doxorubicin + cisplatin	56 (56%)
Oxaliplatin	44 (44%)
Chemotherapy line	
1st	15 (30.6%)
2nd	13 (26.5%)
3rd	21 (42.9%)
Number of PIPAC procedures	
1	21 (42.9%)
2	13 (26.5%)
3 or more	15 (30.6%)
PCI score in patients with multiple PIPAC procedures	
Decreased	10 (37%)
Stable	8 (29.6%)
Increased	9 (33.4%)

Number (frequency); mean ± standard deviation or median (25th; 75th percentiles) and (min–max)

ASA score American Society of Anaesthesiologist's score

Discussion

We studied the outcomes of PIPAC treatment for PC (whatever the etiology) administered alternately with systemic chemotherapy. Of the 28 patients who underwent at least two PIPAC procedures, we observed a regression or at least stabilization of carcinomatosis (in terms of the PCI) in 18 patients (66.6%), and radical R0 surgery with HIPEC was possible for four of them. Among these four patients, two patients underwent total gastrectomy associated with CRS and HIPEC; two others underwent CRS and a HIPEC. All four patients were still alive without recurrence on the date point for the analysis, September 18, 2020. From PC diagnosis, the median overall survival was 29.1 months (14.8–34.3) and it was 11.6 (6–17.3) months from the first PIPAC procedure.

Survival estimates for PC of gastric, colorectal, and ovarian origin were highly heterogeneous. In the literature, Tidadini et al. [14] reported a median survival of 12.8 months for gastric CP. In a meta-analysis of 106 articles or reports on PIPAC, including 45 clinical studies, Alyami et al. [16] reported OS to be between 8 and 15 months for PC of gastric origin, whereas Gockel et al. [20] reported a median OS of between 7 and 15 months depending on the number of PIPAC procedures received (1 or 2, and 3 or more). Thus, our observation of 11.3-month median OS from PC diagnosis is in line with the literature.

For PC of colorectal origin, Ellebæk et al. reported a median survival of 37.6 months from diagnosis of PC and 20.5 months after the first PIPAC procedure [21]. Demtröder et al. found the mean survival to be 15.7 months after the first PIPAC [10]. Here again, our results for this population

Table 2 Systemic chemotherapy

Chemotherapy	1st line Population ($n = 49$)	2nd line Population ($n = 49$)	3rd line Population ($n = 49$)
Yes (%)	49 (100%)	34 (69.4%)	21 (42.9%)
No (%)	0 (0%)	15 (30.6%)	28 (57.1%)
5-Fluorouracil-irinotecan-oxaliplatine-aflibercept	2 (4.1%)	2 (4.1%)	-
Alimta		1 (2%)	-
Alimta-cisplatin	1 (2%)	-	-
Arimidex	-	1 (2%)	-
Avastin		1 (2%)	1 (2%)
Caelyx-yondelis	-	-	1 (2%)
Carboplatine-alimta	1 (2%)	-	-
Carboplatine-paclitaxel-avastin		1 (2%)	-
Docetaxel-cisplatin-5 fluorouracil	1 (2%)	-	-
Folfiri	1 (2%)	2 (4.1%)	1 (2%)
Folfiri-avastin	-	-	1 (2%)
Folfiri-vectibix	-	-	1 (2%)
Folfiri-zaltrap	-	3 (6.1%)	2 (4.1%)
Folfirinox	2 (4.1%)	1 (2%)	-
Folfirinox-avastin	1 (2%)	-	-
Folfox	22 (44.9%)	3 (6.1%)	-
Folfox-avastin	4 (8.2%)	4 (8.2%)	-
Folfox-vectibix	2 (4.1%)	1 (2%)	-
Gemcitabine	-	2 (4.1%)	-
Gemcitabine-cisplatin	-	2 (2%)	-
Gemox	2 (2%)	-	2 (2%)
Gemzar-oxaliplatine	-	2 (4.1%)	-
Gemzar	-	2 (2%)	-
Gemzar-carboplatine	-	-	2 (2%)
Ipilimumab-tilsotolimod	-	-	2 (2%)
Lonsurf	-	-	2 (2%)
Lv5fu2	2 (4.1%)	2 (2%)	2 (4.1%)
Lv5fu2-cisplatine	-	2 (2%)	-
Nivolumab-relatlimab	-	2 (2%)	-
Oxaliplatine-5fu	-	2 (2%)	-
Pembrolizumab c1	2 (2%)	-	-
Regorafenib-switch lonsurf	-	-	2 (2%)
Stivarga	-	-	2 (2%)
Taxol	2 (2%)	2 (2%)	2 (2%)
Taxol-avastin	2 (2%)	2 (2%)	-
Taxol-carboplatine	5 (10.2%)	-	-
Taxol-carboplatine-avastin	-	2 (2%)	-
Taxotere	2 (2%)	-	-
Vectibix	-	2 (2%)	2 (2%)
Xeliri-avastin	-	-	2 (2%)
Xeloda	-	-	2 (2%)
Xeloda 1 2	-	2 (2%)	-

Number (frequency)

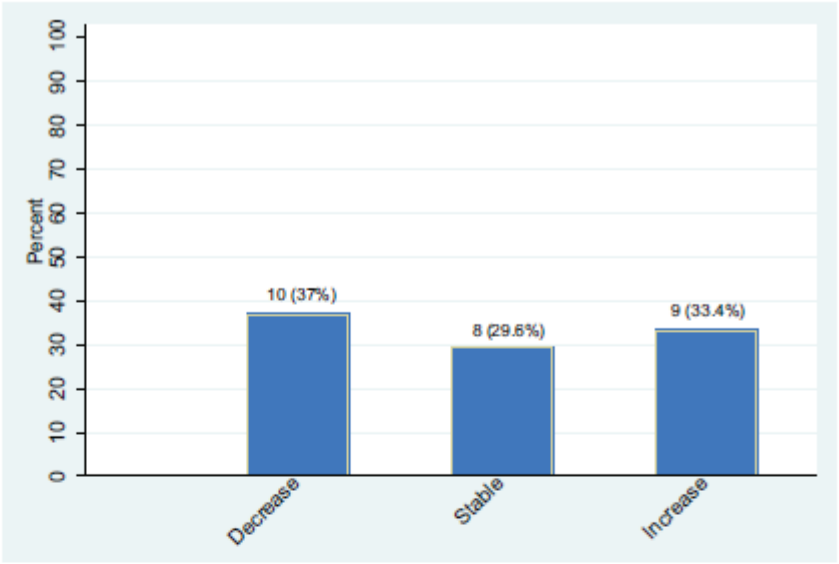


Fig. 1 PCI evolution in patients with multiple PIPAC procedures

were consistent with those reported in the literature. However, for ovarian PC, Alyami et al. [16] estimated a median OS of between 11 and 14 months for ovarian PC, whereas the median OS in our population was 35.5 months (3.2–40.1). For PC of other origins, the number of cases was too low to estimate survival and to compare with the literature.

Subgroup analysis by number of lines of systemic chemotherapy, PIPAC procedures, and timing of PC onset (synchronous or metachronous) in the gastric or colorectal populations did not result in a significant difference in survival.

PIPAC appears to delay oncological progression compared to systemic chemotherapy alone and improves survival [14, 22–25].

There are many limitations to this study: first, it was a single-center retrospective study with a relatively small sample size. Second, there was no historical control group. Third, the group of patients was quite heterogeneous. Two prospective randomized studies (PIPAC associated with systemic chemotherapy vs systemic chemotherapy alone) are currently ongoing in France (PIPAC EstoK 01—NCT04065139) [26] and in Germany (EudraCT 2018–001,035-40) [27] to evaluate the benefit of PIPAC in patients with gastric PC. A third study is currently ongoing in France (PIPACOVA—NCT04811703) [28] to determine the maximum tolerated dose. The results of these studies will provide more information on the effect of PIPAC on overall survival and the maximum tolerated dose in this indication. Large studies are needed in order to conclude on the importance of PIPAC for patients with unresectable PC.

Table 3 Radical surgery

	Whole population ($n=48$)	**Stomach ($n=18$)**	**Ovary ($n=4$)**	**Peritoneal mesothelium ($n=3$)**
Radical R0 surgery after PIPAC	4 (8.3%)	2 (11.1%)	1 (25%)	1 (33.3%)
	$n=4$	$n=2$	$n=1$	$n=1$
Total gastrectomy and cytoreductive surgery *with HIPEC*	2 (50%)	2 (100%)	0 (0%)	0(0%)
Cytoreductive surgery *with HIPEC*	2 (50%)	0(0%)	1 (100%)	1 (100%)
Overall survival from diagnosis of carcinomatosis *(n)*	4 (100%)	2 (100%)	1 (100%)	1 (100%)
Median follow-up (months)	31.3 (16.3–41.4)	32.5 (22.4–42.6)	40.1	l0.2
Overall survival from the first PIPAC session *(n)*	4 (100%)	2 (100%)	1 (100%)	1 (100%)
Median follow-up (months)	28.2 (12.9–39)	29.3 (18.6–40.1)	37.8	7.2
Recurrence-free survival	4 (100%)	2 (100%)	1 (100%)	1 (100%)

Number (frequency); median (25th–75th percentiles)

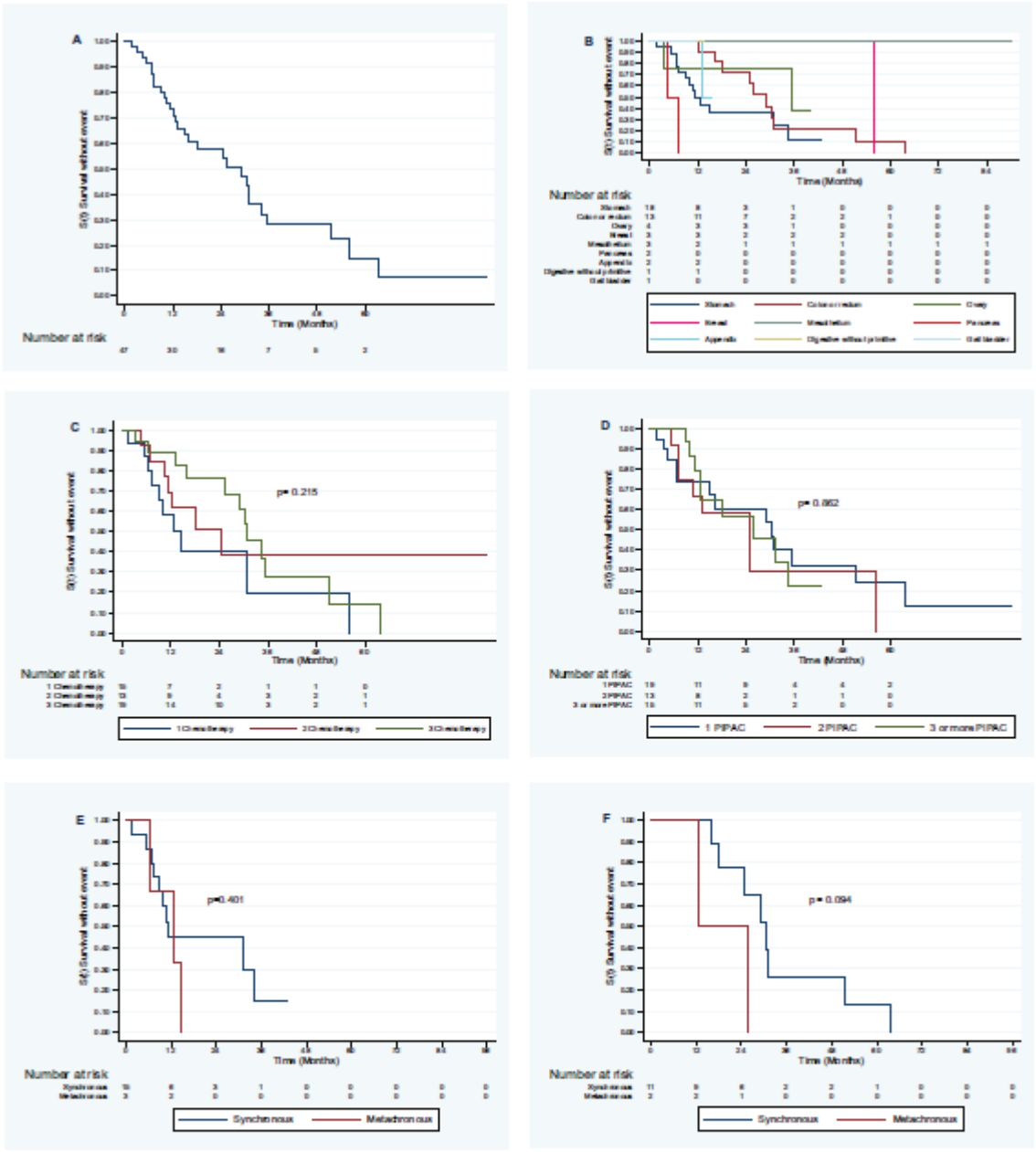


Fig. 2 Kaplan–Meier overall survival curve over the follow-up (from diagnosis of carcinomatosis). **A** Kaplan–Meier overall survival curve over the entire follow-up. **B** Kaplan–Meier overall survival curve by all origin of the carcinomatosis. **C** Kaplan–Meier overall survival curve by number of line of chemotherapy over the entire follow-up. **D** Kaplan–Meier overall survival curve by number of PIPAC over the entire follow-up. **E** Kaplan–Meier overall survival curve by synchronous/metachronous groups with gastric origin. **F** Kaplan–Meier overall survival curve by synchronous/metachronous groups with colorectal origin

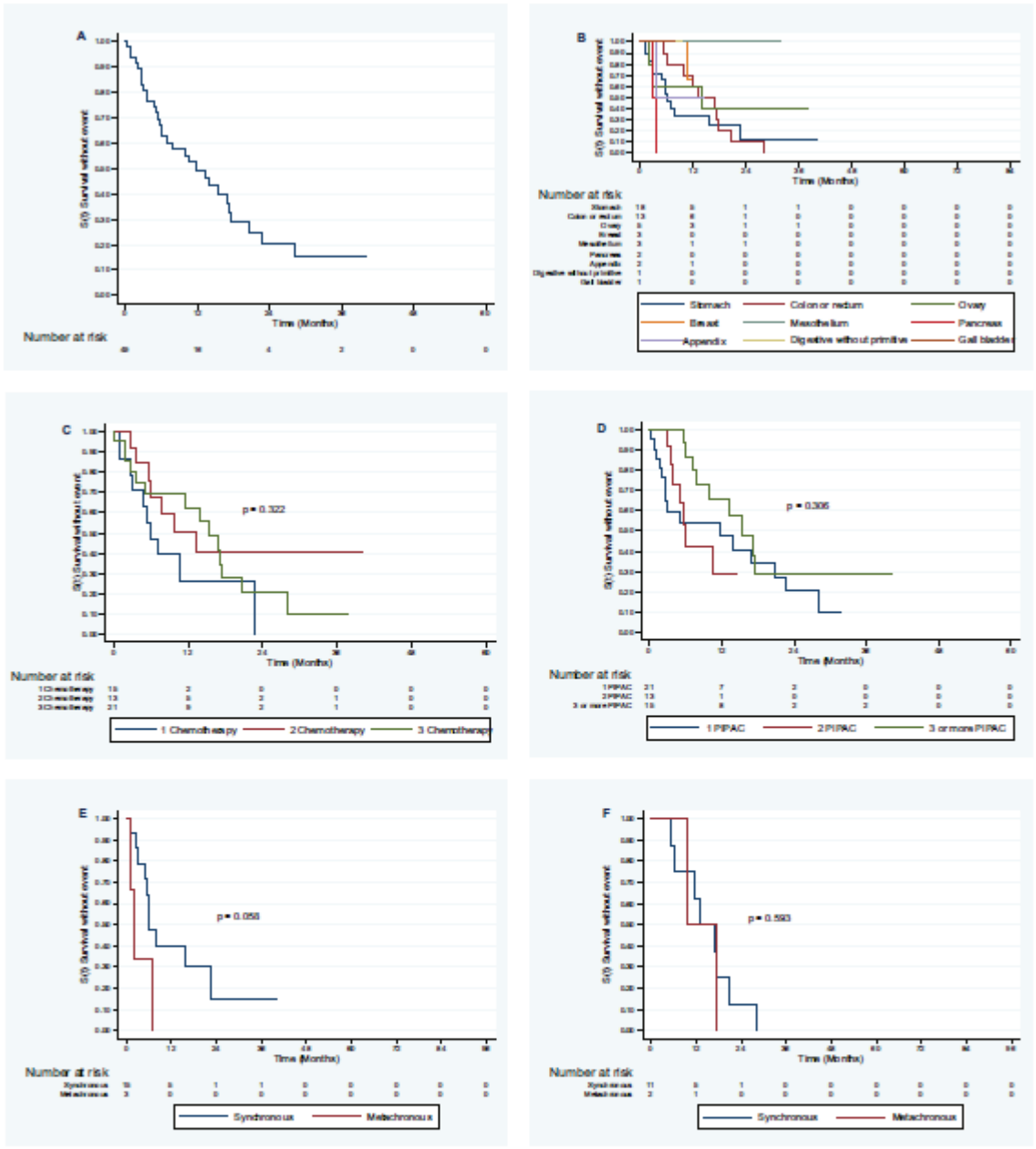


Fig. 3 Kaplan–Meier overall survival curve over the follow-up (from the first PIPAC session). **A** Kaplan–Meier overall survival curve over the entire follow-up. **B** Kaplan–Meier overall survival curve by all origin of the carcinomatosis. **C** Kaplan–Meier overall survival curve by number of line of chemotherapy over the entire follow-up. **D** Kaplan–Meier overall survival curve by number of PIPAC over the entire follow-up. **E** Kaplan–Meier overall survival curve by synchronous/metachronous groups with gastric origin. **F** Kaplan–Meier overall survival curve by synchronous/metachronous groups with colorectal origin

Conclusion

In our experience over 4 years of performing PIPAC, the oncological results have been comparable to those in the literature. The OS was in line with the literature that PIPAC administered alternately with systemic chemotherapy could delay oncological progression and improve survival. These encouraging results justify the ongoing and future evaluations by prospective randomized trials.

Author Contribution Study concept and design: Tidadini, Arvieux. Data acquisition: Tidadini, Abba, Trilling, Bonne, Arvieux. Quality control of data and algorithms: Tidadini, Abba, Arvieux. Data analysis and interpretation: Tidadini, Quesada, Faucheron, Arvieux. Statistical analysis: Quesada. Manuscript preparation: Tidadini, Faucheron, Foote, Arvieux. Manuscript editing: Tidadini, Foote. Manuscript review: all authors.

Declarations

Ethics Approval All procedures performed in this study were in accordance with the ethical standards research committee and with the Helsinki declaration. The study was registered in the internal register of the Grenoble Alpes University Hospital of studies respecting the reference methodology MR004 of the French National Commission for Informatics and Freedoms (CNIL).

Consent to Participate Patients were informed that their anonymized data might in the future be the subject of clinical research and could oppose this by informing the doctor.

Competing Interests The authors declare no competing interests.

References

1. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future. J Gastrointest Oncol. 2016;7(1):143–57. https://doi.org/10.3978/j.issn.2078-6891.2015.112.
2. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016;17(12):1709–19. https://doi.org/10.1016/S1470-2045(16)30500-9.
3. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. J Clin Oncol. 2019;37(23):2028–40. https://doi.org/10.1200/JCO.18.01688.
4. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230–40. https://doi.org/10.1056/NEJMoa1708618.
5. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc. 2012;26(7):1849–55. https://doi.org/10.1007/s00464-012-2148-0.
6. Khomyakov V, Ryabov A, Ivanov A, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum. 2016;1(3):159–66. https://doi.org/10.1515/pp-2016-0017.
7. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. J Gastrointest Surg. 2016;20(2):367–73. https://doi.org/10.1007/s11605-015-2995-9.
8. Tempfer CB, Celik I, Solass W, et al. Activity of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. Gynecol Oncol. 2014;132(2):307–11. https://doi.org/10.1016/j.ygyno.2013.11.022.
9. Tempfer CB, Winnekendonk G, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015;137(2):223–8. https://doi.org/10.1016/j.ygyno.2015.02.009.
10. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis. 2016;18(4):364–71. https://doi.org/10.1111/codi.13130.
11. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clin Exp Metastasis. 2017;34(5):309–14. https://doi.org/10.1007/s10585-017-9849-7.
12. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized intra peritoneal aerosol chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS ONE. 2017;12(10): e0186709. https://doi.org/10.1371/journal.pone.0186709.
13. Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C. First clinical data of pressurized intraperitoneal aerosol chemotherapy (PIPAC) as salvage therapy for peritoneal metastatic biliary tract cancer. Anticancer Res. 2018;38(1):373–8. https://doi.org/10.21873/anticanres.12232.
14. Tidadini F, Abba J, Quesada JL, et al. Effect of pressurized intraperitoneal aerosol chemotherapy on the survival rate of patients with peritoneal carcinomatosis of gastric origin. J Gastrointest Canc. 2021. https://doi.org/10.1007/s12029-021-00698-8.
15. Alyami M, Bonnot PE, Mercier F, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. Eur J Surg Oncol. 2021;47(1):123–7. https://doi.org/10.1016/j.ejso.2020.05.021.
16. Alyami M, Hübner M, Grass F, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20(7):e368–77. https://doi.org/10.1016/S1470-2045(19)30318-3.
17. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74. https://doi.org/10.1007/978-1-4613-1247-5_23.
18. Alyami M, Sgarbura O, Khomyakov V, et al. Standardizing training for pressurized intraperitoneal aerosol chemotherapy. Eur J Surg Oncol. 2020;46(12):2270–5. https://doi.org/10.1016/j.ejso.2020.05.007.
19. Solass W, Kerb R, Mürdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21(2):553–9. https://doi.org/10.1245/s10434-013-3213-1.
20. Gockel I, Jansen-Winkeln B, Haase L, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in gastric cancer patients with peritoneal metastasis (PM): results of a single-center experience and register study. J Gastric Cancer. 2018;18(4):379–91. https://doi.org/10.5230/jgc.2018.18.e37.
21. Ellebæk SB, Graversen M, Detlefsen S, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC)-directed treatment of

peritoneal metastasis in end-stage colo-rectal cancer patients. Pleura Peritoneum. 2020;5(2):20200109. https://doi.org/10.1515/pp-2020-0109.
22. Thomassen I, van Gestel YR, van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. Int J Cancer. 2014;134(3):622–8. https://doi.org/10.1002/ijc.28373.
23. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002;89(12):1545–50. https://doi.org/10.1046/j.1365-2168.2002.02274.x.
24. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27(5):681–5. https://doi.org/10.1200/JCO.2008.19.7160.
25. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012;23(10):2605–12.
26. Eveno C, Jouvin I, Pocard M. PIPAC EstoK 01: pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study. Pleura Peritoneum. 2018;3(2):20180116. https://doi.org/10.1515/pp-2018-0116.
27. Oliver Goetze T, Al-Batran SE, Pabst U, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naïve upper gi-adenocarcinomas with peritoneal seeding - a phase II/III trial of the AIO/CAOGI/ACO. Pleura Peritoneum. 2018;3(2):20180113. https://doi.org/10.1515/pp-2018-0113.
28. History of Changes for Study: NCT04811703. https://www.clinicaltrials.gov/ct2/history/NCT04811703?V_1=View. Accessed 10 May 2022.

5. Effet de la chimiothérapie intrapéritonéale pulvérisée par aérosols sur le taux de survie des patients atteints de carcinose péritonéale d'origine gastrique

Notre étude précédente a montré que la PIPAC pourrait retarder la progression oncologique et donc améliorer la survie. En attendant les résultats de l'étude prospective randomisée, actuellement en cours en Allemagne[54] nous avons comparé les résultats de la PIPAC_CHEM à ceux de ONLY_CHEM chez des patients atteints de CP d'origine gastrique.

RESUME

Introduction : La PIPAC est une nouvelle technique chirurgicale, développée pour le traitement de la carcinose péritonéale initialement non résécable. Notre objectif était de comparer les résultats de la PIPAC associé à une chimiothérapie systémique (PIPAC_CHEM) à ceux de la chimiothérapie systémique seule (ONLY_CHEM) chez des patients atteints de CP gastrique sans métastases autres que péritonéales et en bon état général (indice de performance OMS <3).

Méthode : Il s'agissait d'une étude rétrospective, comparative et non randomisée. Entre juillet 2016 et septembre 2020, 17 patients PIPAC_CHEM ont été comparés à 29 patients ONLY_CHEM. L'objectif principal était la SG à 6 mois à partir du diagnostic de la carcinose.

Résultats : 99 patients ont été sélectionnés et 46 ont été inclus (PIPAC_CHEM, n = 17; ONLY_CHEM, n = 29). Les patients du groupe PIPAC_CHEM étaient significativement plus jeunes (médiane 64 ans [56 ; 68] vs 74 ans [61 ; 79] ; p = 0,005 4). Le nombre de procédures PIPAC par patient était de 2 [1 - 3]. La SG à six mois était significativement plus élevée dans le groupe PIPAC_CHEM que dans le groupe ONLY_CHEM 16/17 (94,1 % [65-99, 2]) vs 19/29 (65,5 % [45,4-79,7]), respectivement ; p = 0,029. Sur l'ensemble du suivi, la médiane de survie [IC 95 %] était de 12,8 mois [7,2-34,3] avec PIPAC vs 9,1 mois [5,4-11,5] sans PIPAC ; p = 0,056. La durée totale des hospitalisations dans les 6 mois suivant le diagnostic de la carcinose, y compris l'hospitalisation nécessaire pour chaque procédure PIPAC et/ou séance de chimiothérapie non ambulatoire, était significativement inférieure pour PIPAC_CHEM (médiane 2 jours [2-7]) que sans PIPAC (médiane 11 jours [3-21]) (p = 0,045).

Conclusion : La SG à 6 mois du diagnostic de carcinose était significativement meilleure pour les patients PIPAC_CHEM que pour les patients similaires traités par chimiothérapie seule. Cette différence semble se poursuivre jusqu'à au moins 18 mois. Ces résultats encourageants justifient une évaluation par des essais prospectifs et randomisés.

Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-021-00698-8

ORIGINAL RESEARCH

Effect of Pressurized Intraperitoneal Aerosol Chemotherapy on the Survival Rate of Patients with Peritoneal Carcinomatosis of Gastric Origin

Fatah Tidadini[1,2] · Julio Abba[1] · Jean-Louis Quesada[3] · Magalie Baudrant[1] · Aline Bonne[1] · Alison Foote[3] · Jean-Luc Faucheron[1] · Olivier Glehen[2] · Laurent Villeneuve[2] · Catherine Arvieux[1,2]

Accepted: 20 August 2021

Abstract

Introduction Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new surgical technique for the treatment of initially unresectable peritoneal carcinomatosis (PC). Our objective was to compare the results of PIPAC associated with systemic chemotherapy (PIPAC_CHEM) with those of systemic chemotherapy alone (ONLY_CHEM) in patients with gastric PC without metastasis other than peritoneal, and the WHO performance status < 3.

Methods This was a retrospective, single center, comparative non-randomized study. Seventeen PIPAC_CHEM patients were compared to 29 ONLY_CHEM patients. The primary endpoint was overall survival at 6 months from diagnosis of PC.

Results Ninety-eight patients were screened and 46 were included (PIPAC_CHEM, $n = 17$; ONLY_CHEM, $n = 29$). The PIPAC_ CHEM population was significantly younger (median 64 years [56; 68] vs 74 years [61; 79]; $p = 0.0054$). Median PIPAC session per patient is 2 [1–3]. Six-month survival was significantly higher in the PIPAC_CHEM group than in the ONLY_CHEM group 16/17 (94.1% [65–99.2]) vs 19/29 (65.5% [45.4–79.7]), respectively; $p = 0.029$. Over the entire follow-up, median survival [95% CI] was 12.8 months [7.2–34.3] with PIPAC vs 9.1 months [5.4–11.5] without, $p = 0.056$.
At 6 months, median length of additional hospitalization was significantly less for PIPAC_CHEM (median 2 days [2–7]) than without PIPAC (median 11 days [3–21]) ($p = 0.045$).

Conclusion The overall survival at 6 months after the diagnosis of carcinomatosis was significantly better for PIPAC_CHEM patients. This difference appears to continue until at least 18 months. At 6 months, days of additional hospitalization was significantly less in the PIPAC_CHEM group.

Trial Registration Clinicaltrials.gov Identifier: NCT 04,879,953

Keywords Pressurized intraperitoneal aerosol chemotherapy (PIPAC) · Peritoneal carcinoma · Gastric cancer · Overall survival · Systemic chemotherapy

Introduction

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer deaths [1]. Peritoneal carcinomatosis (PC) is a very common manifestation in advanced adenocarcinoma-type gastric cancer [2]. Without intervention, the prognosis is poor with survival of only a few months (median, 3.1 months) [3, 4]. Standard treatment is based on systemic chemotherapy; however, the pharmacokinetics of drug delivery to the peritoneum is poor with limited efficacy compared to other metastatic sites such as the liver or lung [5]. When the carcinomas are resectable, selected patients can benefit from locoregional therapeutic approaches combining peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC), offering a significant improvement in survival [6, 7].

In 2012, Reymond et al. described a new approach for initially unresectable cases, consisting of applying chemotherapy agents directly to the peritoneum using a pressurized

✉ Catherine Arvieux
carvieux@chu-grenoble.fr

1 Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, Grenoble, France

2 Lyon Center for Innovation in Cancer- EA 3738, Lyon 1 University, Lyon, EA, France

3 Clinical Pharmacology Unit, INSERM CIC 1406, Grenoble Alpes University Hospital, Grenoble, France

Published online: 22 October 2021

aerosol, known as pressurized intraperitoneal aerosol chemotherapy (PIPAC) [8]. The use of this technique results in a higher local drug concentration compared to standard intraperitoneal or intravenous chemotherapy. The aim of this innovative therapy is to improve survival while preserving quality of life, but a further advantage is that it can render the PC resectable, more accessible to complete cytoreductive surgery (CRS). PIPAC has been applied to PC of all origins. Several recent studies have provided evidence that a treatment regimen combining PIPAC and systemic chemotherapy improves survival without adversely affecting quality of life [9–12]. However, in the absence of published prospective controlled trials, a clear advantage of this treatment regimen over systemic chemotherapy alone has not been established and the results in terms of efficacy and the benefit/risk ratio of this procedure remain debated. We conducted a retrospective study (PIPAC_GRE) comparing the results of PIPAC administered alternately with systemic chemotherapy (PIPAC_CHEM) versus systemic chemotherapy alone (ONLY-CHEM) in patients with non-resectable gastric PC eligible for non-palliative treatment. The main objective was overall survival at 6 months from diagnosis of carcinomatosis. Secondary objectives were the total duration of any additional hospitalization up to 6 months after the diagnosis of carcinomatosis, overall survival throughout the study follow-up from the diagnosis of carcinomatosis and from the diagnosis of the primary tumor.

Methods

This was a retrospective, comparative, and non-randomized study performed at the Grenoble Alpes University Hospital, a center with expertise in the PIPAC technique, between July 2016 and September 2020. The study population consisted of adult patients with adenocarcinoma-type gastric non-resectable PC, without metastasis other than peritoneal, treated either with PIPAC administered in alternation with systemic chemotherapy (PIPAC_CHEM) or by systemic chemotherapy alone (ONLY_CHEM). All patients receiving PIPAC in our hospital during the study period were included. The patients in the ONLY_CHEM control group had been treated during the same period and were carefully selected according to age, general state of health (the WHO performance status < 3), and absence of extra-peritoneal metastases so as to be as similar as possible to the patients in the PIPAC group. Patient vital status of was determined from medical records and from phone calls, using September 18, 2020, as the point date. The times were calculated from the dates of diagnosis of carcinomatosis and of the primary tumor. Days of hospitalization, in addition to those for treatment purposes, during the first 6 months after the diagnosis of carcinomatosis were summed.

The Oncology Strategy

PIPAC procedures were performed every 6 to 8 weeks, alternating with systemic chemotherapy, replacing a cycle of intravenous chemotherapy. The treatment strategy and systemic chemotherapy used between PIPAC procedures and in the control group (ONLY_CHEM) had been decided by a multidisciplinary committee. Tumor response was based on surgical assessment using the peritoneal cancer index (PCI) [13], routine intraoperative biopsies, and regular CT scans of the abdomen and chest.

Surgical Procedure and PIPAC

All surgeons involved in PIPAC procedures had completed PIPAC training [14]. Procedures were performed in a dedicated operating room with a team of specialist operating room nurses assigned to PIPAC procedures. A safety checklist established before the first intervention jointly by the surgeons, the operating room nurses, and the pharmacist was used at the 3 different stages of each procedure.

PIPAC procedures were performed as previously described [8, 15]. Briefly, under general anesthesia, a laparoscopy was performed using an open laparoscopic technique to prevent intestinal wounds, which would contraindicate the procedure. A 12-mmHg pneumoperitoneum was created, and to ensure the safety of the procedure, the pressure of the pneumoperitoneum was maintained constant throughout the procedure. Two laparoscopic balloon trocars (of 11 and 12 mm) were used. A thorough exploration of the abdomen, peritoneal cancer index assessment, peritoneal biopsies, and ascites cytology (in the case of ascites) were performed prior to administration of the chemotherapy aerosol.

The precise drug administration protocol for PIPAC was established in consultation with the specialized hospital pharmacist. For carcinomas of gastric origin, doxurubicin at a dose of 1.5 mg/m^2 was administered in combination with cisplatin 7.5 mg/m^2 diluted in 40 and 150 mL of 0.9% sodium chloride, respectively. In the case of contraindication, oxaliplatine at a dose of 92 mg/m^2 in a 5% dextrose solution was recommended.

A CE certified CAPNOPEN® nebulizer (Reger Medizintechnik GmbH, Villingendorf, Germany) connected to a high pressure injector was inserted through the trocars. Nebulization of the drug was initiated by a remote control after all the staff had left the operating room. The nebulizer aerosolized the fluids at 30 mL/min with a maximum pressure of 20 bars over 5 min. After 30 min of application, the CO_2 and remaining toxic aerosols were evacuated by a closed air evacuation system. The safety checklist was systematically verified before administration of the drug, at the end of the procedure, and signed by the surgeon in charge and the operating room nurse.

Follow-up

Following each PIPAC procedure patients was kept under surveillance for at least 24 h and a blood sample was taken on day 1. Early mobilization and nutrition were standard for all patients. All signs of toxicity and/or postoperative complications occurring during the first 6 postoperative months were graded according to the Clavien-Dindo classification [16], with grades 3 to 5 corresponding to major complications. All patients (including the ONLY-CHEM control group) had a standard oncology follow-up with regular CT scans, tumor marker tests, and clinical examinations.

Statistical Analysis

Continuous data are presented using descriptive statistics: median and [25th–75th percentiles]). Categorical data are presented using frequencies and percentages. Quantitative parameters were compared between groups using a Student's *t* test, or a Mann–Whitney test when normality was rejected. Qualitative parameters were compared using the Chi-square test or otherwise a Fisher's exact test, as applicable.

Overall survival (OS) was defined as the time from the date of PC diagnosis until death due to any cause.

Survival rates were calculated using the Kaplan–Meier method. Overall survival at 6 months by treatment group was compared using a log-rank test. The role of confounding factors was explored using univariate Cox proportional risk models.

A Cox proportional hazard multivariate model, with backward-stepwise selection (and a 20% threshold), was used to evaluate overall survival at 6 months for each treatment group.

A threshold of 5% was used to define the significance of the statistical tests. No adjustment for multiplicity was applied. Statistical analysis was performed using Stata software version 14.2 (STATA, StataCorp, Texas, USA).

Results

Patients' Characteristics

Out of 98 consecutive patients presenting with non-resectable gastric PC between July 2016 and September 2020, 52 (53.1%) were excluded from the analysis (28 for extra-peritoneal metastases, 9 too weak to be treated, 9 for missing dates of diagnosis and/or death, and 6 for gastrointestinal stromal tumors). Forty-six (46.9%) treated patients were included on the study; seventeen had received PIPAC (PIPAC_CHEM) and 29 controls had received systemic chemotherapy only (CHEM_ONLY) (Fig. 1).

The demographic data of all individuals included in the study, the characteristics of the tumors and carcinomatosis, and any previous surgery for cancer are presented on (Table 1) and supplementary eTable 1. Twenty-eight patients were male (60.9%). At the time of diagnosis of carcinomatosis: the median age was 68.5 [57–74], and median BMI was 22.0 [19.1–26]. Twenty-four patients (52.2%) had presented an undifferentiated adenocarcinoma and 27 PC (58.7%) were classed as synchronous. All patients had received at least one line of intravenous chemotherapy (Table 2). The patients in the two groups (PIPAC_CHEM and ONLY_CHEM) were comparable for all characteristics except age, with the PIPAC_CHEM group being significantly younger (median 64 years [56–68] vs 73.5 years [61–79]; $p=0.005$). The 17 PIPAC_CHEM patients underwent a total of 42 PIPAC procedures, with a median of 2 procedures [1; 3] and median PCI at the start of treatment of 18 [12–20].

Overall Survival

Overall survival at 6 months after primary tumor diagnosis was not significantly different between PIPAC_CHEM and ONLY_CHEM groups (16/17 (94.1%) vs 25/29 (86.2%); $p=0.391$). Over the entire follow-up, the median survival [95% CI] in the PIPAC_CHEM group was 31 months [9.8–75.5] vs. 13.6 [11–23.5]; with OS rates [95% CI] at 12, 18, and 24 months of 64.2% [36.9–82.1], 57.8% [31.1–77.3], and 51.3% [25.7–72.1] vs 62.1% [42.1–76.9], 36.5% [19.5–53.8], and 21.9% [9–38.5], respectively (Fig. 2). In contrast, from the diagnosis of carcinomatosis, the 6-month survival rate [95% CI] was significantly better for PIPAC_CHEM vs ONLY_CHEM groups: 16/17 (94.1% [65–99.2]) vs 19/29 (65.5% [45.4–79.7]), respectively; $p=0.029$. From carcinomatosis diagnosis, over the entire follow-up the median survival [95% CI] in the PIPAC_CHEM group was 12.8 months [7.2–34.3] versus 9.1 months [5.4–11.5] for the ONLY_CHEM group ($p=0.056$), with OS rates [95% CI] at 12, 18, and 24 months of 94.1% [65–99.2], 51.8% [26.2–72.4], and 38.8% [16.3–61.1] vs 66.7% [46.9–80.5], 31.8% [15.9–48.9], and 15.9% [5.2–32], respectively (Fig. 3).

Duration of Hospitalization Up to 6 Months After Diagnosis of Carcinomatosis

For the whole study population, the median total length of hospitalization up to 6 months after diagnosis of PC was 7 days [2–17] including the hospitalization needed for each PIPAC procedure and/or non-ambulatory chemotherapy session. As shown in Fig. 4, patients in the PIPAC_CHEM group had a shorter total length of hospitalization at 6 months compared to the ONLY_CHEM group (median 2 [2–7] days vs 11 [3–21]; $p=0.045$).

Radical Surgery After Treatment

Radical surgery after PIPAC_CHEM was possible in 2/17 (11.8%) cases vs 3/29 (10.3%) for ONLY_CHEM patients, $p=1.000$; (eTable 2 in supplement).

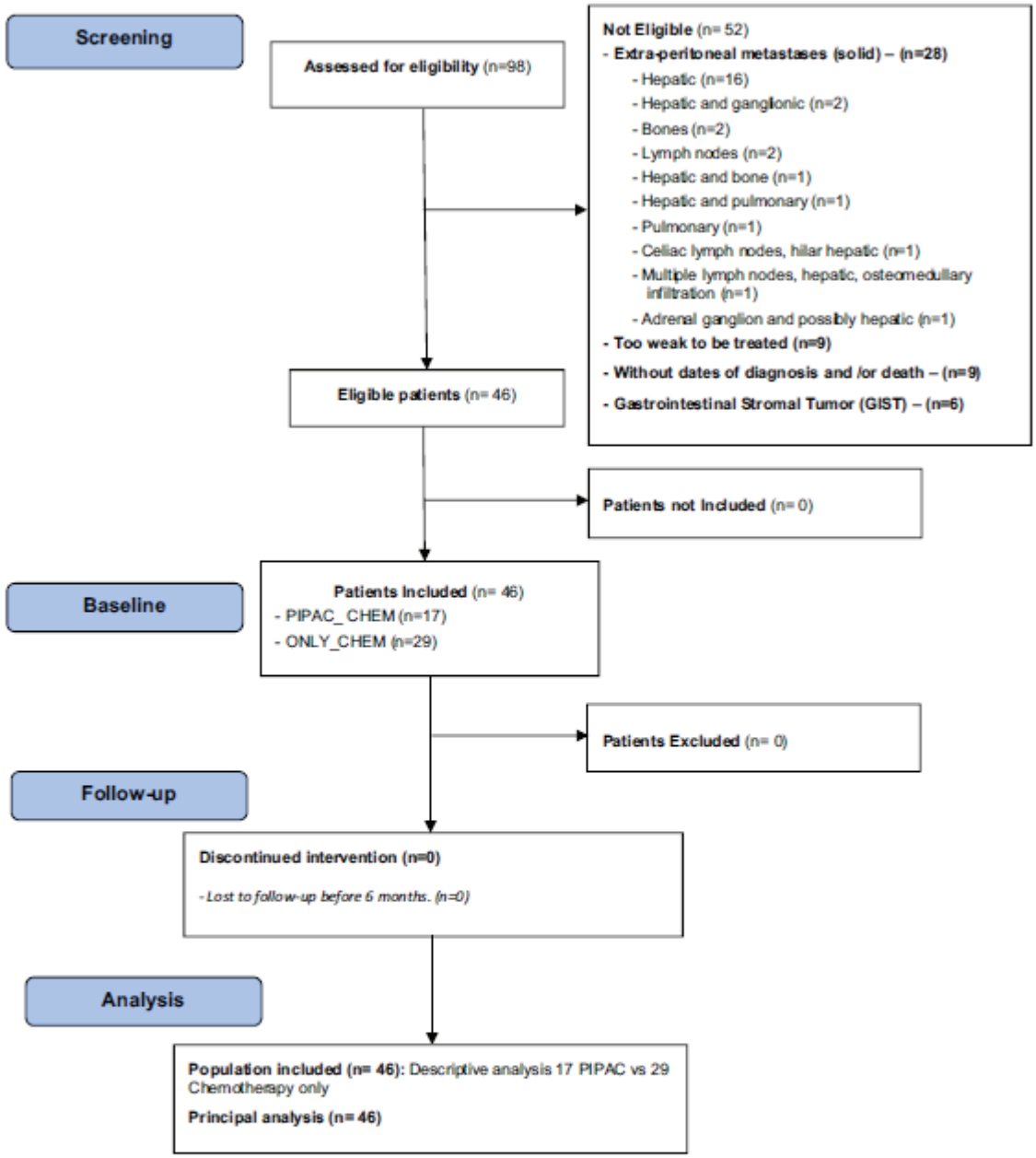


Fig. 1 Flow diagram

Major Complications Classified Clavien-Dindo 3b or 4, Over the Entire Follow-up (from Diagnosis of Carcinomatosis)

The number of major complications classified Clavien-Dindo 3b or 4 in the PIPAC_CHEM group was 2/17 (11.8%) versus 2/29 (6.9%) for the ONLY_CHEM group; $p = 0.619$. In the PIPAC_CHEM group the two major complications were a case of obstructive jaundice that was operated by laparotomy and a case of hemorrhagic shock requiring intensive care. In the ONLY_CHEM group, one patient had an exploratory laparotomy for cardiac arrest due to a coronary

Table 1 Demographic and medical characteristics

	Population $n=46$	PIPAC_CHEM $n=17$	ONLY_CHEM $n=29$	*p*-value
Age	68.5 [57–74]	64 [56–68]	74 [61–79]	0.005[4]
Sex (male)	28 (60.9%)	10 (58.8%)	18 (62.1%)	0.828[1]
BMI	22 [19.1–26]	21.3 [18.6–24.7]	22.2 [20.4–27.4]	0.407[3]
WHO performance status				0.111[2]
0	7 (15.6%)	5 (29.4%)	2 (7.1%)	
1	25 (55.6%)	7 (41.2%)	18 (64.3%)	
2	13 (28.9%)	5 (29.4%)	8 (28.6%)	
Cancer history				
Other type of cancer	10 (21.7%)	3 (17.7%)	7 (24.1%)	0.723[2]
Gastrectomy before carcinomatosis	10 (21.7%)	2 (11.8%)	8 (27.6%)	0.282[2]
Partial	3 (30%)	0 (0%)	3 (37.5%)	1.000[2]
Total	7 (70%)	2 (100%)	5 (62.5%)	
Peritoneal carcinomatosis				0.210[1]
Synchrone	27 (58.7%)	12 (70.6%)	15 (51.7%)	
Metachrone	19 (41.3%)	5 (29.4%)	14 (48.3%)	
Differentiated adenocarcinoma	22 (47.8%)	8 (47.1%)	14 (48.3%)	0.936[1]
Time between metachrone carcinomatosis and primitive tumor diagnosis (days)	270 [142–719] $n=19$	362 [230–1845] $n=5$	240.5 [142–661] $n=14$	0.517[4]
Number of hospital stays 6 months after diagnosis of carcinomatosis	1 [1–2]	1 [1–1]	1 [1–2]	0.288[4]
Number of PIPAC procedures	2 [1–3]	2 [1–3]	-	-
Initial PCI	18 [12–20]	18 [12–20]	-	-

Median with [25th–75th percentiles], frequency (number), Chi-square test[1], Fisher exact test[2], Student *t*-test[3], Mann–Whitney test[4]

spasm and another exploratory laparotomy for occlusion (Table 3).

Multivariate Analysis

We looked for confounding factors on which it would be interesting to adjust the comparison of 6-month survival between groups. The significance threshold for the selection of these parameters was set at 20%. Univariate analyses using a Cox model were performed on the following risk factors: age, sex, BMI, the WHO performance status, previous gastrectomy, histology of the primary tumor, chronology of onset of carcinomatosis, and time to diagnosis of cancer (eTable 3). The analyses were not performed on the PCI

Table 2 Systemic chemotherapy

Chemotherapy	Whole study population $n=46$	PIPAC_CHEM $n=17$	ONLY_CHEM $n=29$	*p*-value
FOLFOX	30 (65.2%)	14 (82.4%)	16 (55.2%)	0.062[1]
FOLFIRI	2 (4.4%)	0 (0%)	2 (6.9%)	0.524[2]
LV5FU2	5 (10.9%)	3 (17.7%)	2 (6.9%)	0.343[2]
FU	4 (8.7%)	0 (0%)	4 (13.8%)	0.281[2]
TAXOL	7 (15.2%)	1 (5.9%)	6 (20.7%)	0.234[2]
RAMUCIRUMAB	2 (4.4%)	1 (5.9%)	1 (3.5%)	1.000[2]
OXALIPLATINE	5 (10.9%)	1 (5.9%)	4 (13.8%)	0.637[2]
FLUORURACILE	1 (2.2%)	1 (5.9%)	0 (0%)	0.370[2]
CISPLATINE	2 (4.4%)	1 (5.9%)	1 (3.5%)	1.000[2]
TAXOTERE	1 (2.2%)	1 (5.9%)	0 (0%)	0.370[2]
HERCEPTIN	1 (2.2%)	0 (0%)	1 (3.5%)	1.000[2]
CARBOPLATINE	2 (4.4%)	0 (0%)	2 (6.9%)	0.524[2]
DOCETAXEL	2 (4.4%)	0 (0%)	2 (6.9%)	0.524[2]

Frequency(Number), Chi-square test[1], Fisher exact test[2]

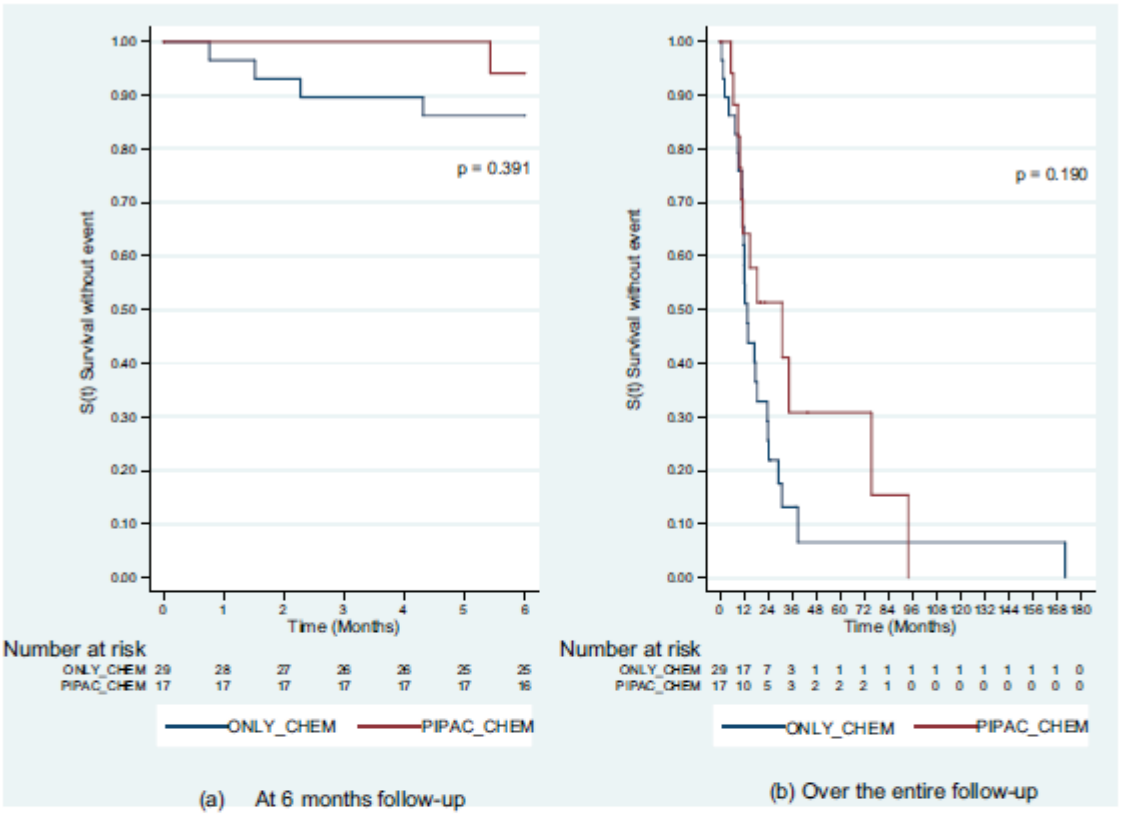


Fig. 2 Kaplan–Meier survival estimates from diagnosis of primary tumor

risk factor because ONLY-CHEM patients did not have an exploratory laparoscopy (thus, a PCI score was not available for patients in this group). None of these parameters emerged as a risk factor, except for the WHO performance status that was retained as a confounding factor, probably linked to death within 6 months (HR [95% CI], 1.93 [0.75; 4.98]); see eTable 4 in supplement. The comparison of overall survival at 6 months between the chemotherapy groups before ($p=0.062$) or after adjustment for the WHO performance status ($p=0.062$) using the multivariate Cox model suggests a protective trend of PIPAC treatment associated with systemic chemotherapy compared to systemic chemotherapy alone (HR [95% CI], 0.141 [0.018; 1.104]) but was not statistically significant; see eTable 4 in supplement.

Discussion

In this non-randomized retrospective study, we compared overall survival following two strategies of treatment for selected patients with adenocarcinoma-type gastric cancer and unresectable peritoneal carcinomatosis. Each patient's treatment strategy had been decided by a multidisciplinary committee. All 46 patients eligible for this study were eligible for PIPAC, however, given the innovative nature of the treatment and the lack of knowledge on the possible complications of PIPAC in the first years following its introduction (2016 to 2018) and so as to avoid three interventions under general anesthetic in a period of 4 months for aged fragile patients our multidisciplinary committee tended to be reticent about a PIPAC strategy in older patients or those with a history of other types of cancer. This explains the difference in age between the two groups.

Treatment with PIPAC given alternately with systemic chemotherapy provided a significant difference ($p=0.029$) in OS at 6 months [95% CI] after diagnosis of PC compared with systemic chemotherapy alone (94.1% [65–99.2] and 65.5% [45.4–79.7], respectively). The number of days of hospitalization, including those required for each PIPAC procedure and/or non-ambulatory chemotherapy session, at 6 months were significantly fewer in the PIPAC_CHEM group ($p=0.045$).

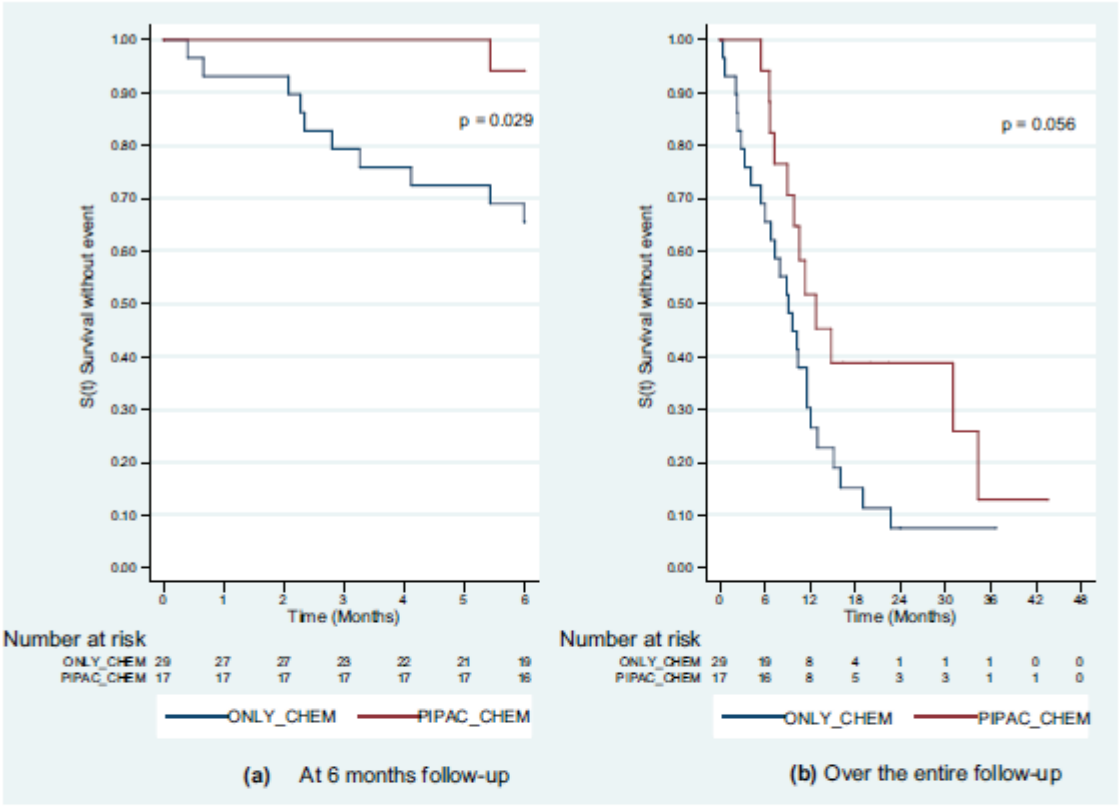


Fig. 3 Kaplan–Meier survival estimates from diagnosis of carcinomatosis

After a median follow-up of 10.2 months (0.4, 43.6) from diagnosis of PC for the entire study population (see supplementary eTable 5), the median survival was longer in the PIPAC_CHEM group (difference 3.7 months). PIPAC appears to delay oncologic progression with a significant effect on 6-month survival that appears to continue for at least 18 months. The characteristics of the carcinomatosis, of the tumor, any previous gastrectomy, and any previous cancer were not significantly different between the groups; however, the latter might appear to be more frequent in the ONLY_CHEM group. PIPAC treatment appears most promising in the medium term. In a meta-analysis of 106 articles or case reports of PIPAC, including 45 clinical studies, Alyami et al. [12] reported OS to be between 8 and 15 months. In their recent study, the same author reports survival of 19.1 months [11]. Thus, our result (median survival [95% CI] of 12.8 months [7.2–34.3]) appears to be in line with most of the published studies. However, whatever the treatment strategy, the long-term prognosis remains poor.

The median survival [95% CI] from diagnosis of PC seen in our study, with chemotherapy alone (9.1 months [5.4–11.5]), is in the same range as that reported in the literature. Thomassen et al. estimated survival [95% CI] to be 8.0 months [6.8–9.3], and 9.9 months [7.7–11.8] for patients having undergone primary tumor resection [17]. A direct comparison is difficult due to the heterogeneous treatments in our ONLY_CHEM group, including chemotherapy and resection of the primary tumor (8 (27.6%)), and also due to the evolution over time of chemotherapy protocols for this indication.

Among the patients who were still alive at the date point (September 18, 2020), two patients in the PIPAC_CHEM group have had total gastrectomy associated with CRS and HIPEC; and in the ONLY_CHEM group, one patient has undergone partial gastrectomy associated with CRS and HIPEC, and another has had CRS without HIPEC (due to his age and comorbidities). A third patient in this group had died following a total gastrectomy associated with CRS and HIPEC.

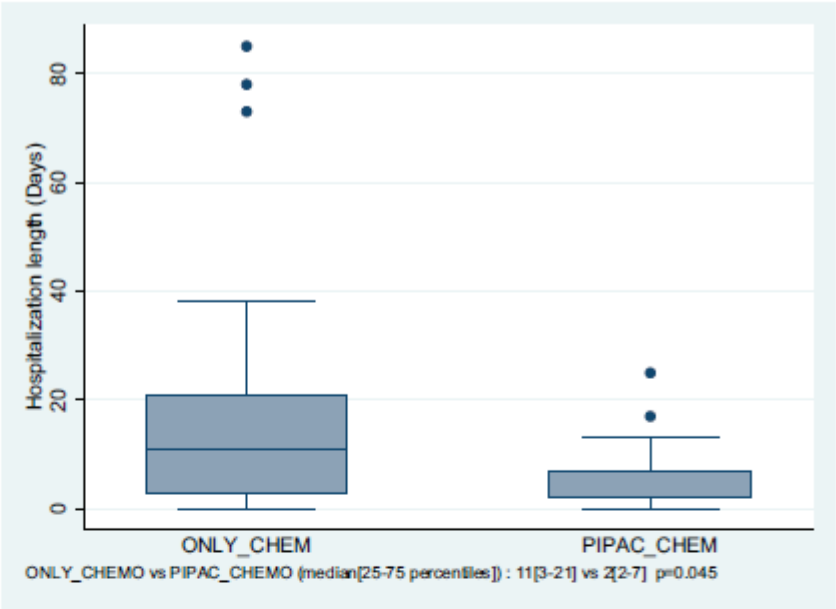


Fig. 4 Comparison of days of hospitalization up to 6 months follow-up (from diagnosis of carcinomatosis)

The number of major complications classified as Clavien-Dindo 3b or 4 ($p=0.619$) and the number of hospital stays ($p=0.288$), respectively, over the entire follow-up and at 6 months after the diagnosis of carcinomatosis did not show any significant difference between the 2 groups. Undergoing PIPAC treatment does not appear to affect the quality of life of patients.

Our study has some limitations: first, it was a single-center retrospective study with a relatively small sample size. Second, it was the absence of randomization. Two prospective randomized studies (PIPAC associated with systemic chemotherapy vs systemic chemotherapy alone) are currently ongoing in France (PIPAC EstoK 01- NCT04065139) [18] and in Germany (EudraCT 2018–001,035-40) [19] to evaluate the benefit of PIPAC in patients with gastric PC. The results of these studies will provide more information on the effect of PIPAC on overall survival in this indication.

Table 3 Major complications classified Clavien-Dindo 3b or 4, over the entire follow-up (from diagnosis of carcinomatosis to date point)

Type of complication	Complication	Whole study population ($n=46$)	PIPAC_CHEM ($n=17$)	ONLY_CHEM ($n=29$)	p-value
Event during care Clavien-Dindo = 3b or 4		4 (8.7%)	2 (11.8%)	2 (6.9%)	0.619[2]
Life-threatening complication requiring critical care management Clavien-Dindo = 4	Hemorrhagic shock *n* (%)	1 (2.2%)	1 (5.9%)	0 (0.0%)	0.370[2]
Intervention under general anesthesia Clavien-Dindo = 3b	Obstructive jaundice operated by laparotomy n (%)	1 (2.2%)	1 (5.9%)	0 (0.0%)	0.370[2]
	Exploratory laparotomy for cardiac arrest due to a coronary spasm n (%)	1 (2.2%)	0 (0.0%)	1 (3.5%)	1.000[2]
	Exploratory laparotomy for occlusion n (%)	1 (2.2%)	0 (0.0%)	1 (3.5%)	1.000[2]

Number (frequency, %), Chi square test[1], Fisher exact test[2]

Conclusion

In this retrospective study, overall survival at 6 months after the diagnosis of carcinomatosis was significantly better for patients who received PIPAC than for similar patients treated with chemotherapy alone; and this difference appears to persist until at least 18 months. The significantly shorter total length of hospitalization for the PIPAC group suggests that this strategy may be the most appropriate for the treatment of gastric PC. These encouraging results justify further evaluation by prospective randomized trials that include quality of life and medico-economic analyses.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12029-021-00698-8.

Author Contribution Study concept and design: Tidadini, Glehen, Villeneuve, and Arvieux. Data acquisition: Tidadini, Abba, and Arvieux. Quality control of data and algorithms: Tidadini, Abba, Bonne, Baudrant, and Arvieux. Data analysis and interpretation: Tidadini, Abba, Quesada, Faucheron, Foote, and Arvieux. Statistical analysis: Quesada. Manuscript editing: Tidadini, Foote, Bonne, and Arvieux. Manuscript review: all authors.

Availability of Data and Material (Data Transparency) Anonymized patient data will be made available on reasonable request for academic use after publication of the article and with a signed contract between the applicant and Grenoble Alpes University Hospital.

Declarations

Ethics Approval Study ethical approval was obtained on 03.02.2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891) and was registered in the CHU Grenoble Alpes register of studies respecting the reference methodology MR004 of the National Commission for Informatics and Liberties (CNIL).

Informed Consent Patients were informed that their anonymized data might in the future be the subject of a research protocol and could oppose this by informing the doctor.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Coccolini F, Cotte E, Glehen O, Lotti M, Poiasina E, Catena F, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol. 2014;40:12–26.
3. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88:358–63.
4. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future. J Gastrointest Oncol. 2016;7:143–57.
5. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016;17:1709–19.
6. Bonnot P-E, Piessen G, Kepenekian V, Decullier E, Pocard M, Meunier B, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. J Clin Oncol. 2019;37:2028–40.
7. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378:230–40.
8. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc. 2012;26:1849–55.
9. Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum. 2016;1:159–66.
10. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond M-A. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. J Gastrointest Surg. 2016;20:367–73.
11. Alyami M, Bonnot P-E, Mercier F, Laplace N, Villeneuve L, Passot G, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. Eur J Surg Oncol. 2021;47:123–7.
12. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20:e368–77.
13. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
14. Alyami M, Sgarbura O, Khomyakov V, Horvath P, Vizzielli G, So J, et al. Standardizing training for Pressurized Intraperitoneal Aerosol Chemotherapy. Eur J Surg Oncol. 2020;46:2270–5.
15. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553–9.
16. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
17. Thomassen I, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. Int J Cancer. 2014;134:622–8.
18. Eveno C, Jouvin I, Pocard M. PIPAC EstoK 01: Pressurized Intra-Peritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study. Pleura Peritoneum. 2018;3:20180116.
19. Oliver Goetze T, Al-Batran S-E, Pabst U, Reymond M, Tempfer C, Bechstein WO, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naïve upper gi-adenocarcinomas with peritoneal seeding - a phase II/III trial of the AIO/CAOGI/ACO. Pleura Peritoneum. 2018;3:20180113.

Online data supplement

Contents

e-Table 1 – Medical history other than cancer, prior to PIPAC

	Population n =46	PIPAC_CHEM n =17	ONLY_CHEM n =29	p-value
Medical history				
COPD / Respiratory pathology	13 (28.3%)	4 (23.5%)	9 (31%)	0.739(2)
Dyslipidemia	7 (15.2%)	2 (11.8%)	5 (17.2%)	1.000(2)
Hypertension	15 (32.6%)	5 (29.4%)	10 (34.5%)	0.723(1)
Cardiopathy	5 (10.9%)	1 (5.9%)	4 (13.8%)	0.640(2)
Stroke	1 (2.2%)	1 (5.9%)	0 (0.0%)	0.370(2)
Atrial fibrillation	4 (8.7%)	2 (11.8%)	2 (6.9%)	0.619(2)
Peripheral artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Deep vein thrombosis / pulmonary embolism	2 (4.4%)	1 (5.9%)	1 (3.5%)	1.000(2)
Diabetes	6 (13%)	1 (5.9%)	5 (17.2%)	0.390(2)
Renal failure	4 (8.7%)	1 (5.9%)	3 (10.3%)	1.000(2)
Hepathopathy	2 (4.4%)	1 (5.9%)	1 (3.5%)	1.000(2)
Abdominal Surgery	13 (28.3%)	4 (23.5%)	9 (31%)	0.739(2)
Other medical history	34 (73.9%)	15 (88.2%)	19 (65.5%)	0.163(2)

Median with [25th - 75th percentiles], Frequency(Number)
Chi-2 test(1), Fisher-exact test(2)

eTable 2. Radical surgery after treatment

	Whole study Population n =46	PIPAC_CHEM n =17	ONLY_CHEM n =29	p-value
Total gastrectomy and cytoreductive surgery	5 (10.9%)	2 (11.8%)	3 (10.3%)	1.000(2)
Total gastrectomy and cytoreductive surgery with HIPEC	3 (6.5%)	2 (11.8%)	1 (3.5%)	0.545(2)
Partial gastrectomy and cytoreductive surgery with HIPEC	1 (2.2%)	0 (0%)	1 (3.5%)	1.000(2)
Partial gastrectomy and cytoreductive surgery without HIPEC	1 (2.2%)	0 (0%)	1 (3.5%)	1.000(2)

Frequency (Number), Chi-2 test (1), Fisher-exact test (2),
HIPEC: Hyperthermic Intraperitoneal Chemotherapy

eTable 3. - Univariate analysis

	Hazard Ratio	p-value
Age (years)	1.02 [0.97 ; 1.08]	0.380[5]
BMI (kg/m²)	0.96 [0.83 ; 1.11]	0.593[5]
Sex (Female)	0.56 [0.15 ; 2.09]	0.385[5]
WHO Performance Status	1.93 [0.75 ; 4.98]	0.175[5]
Gastrectomy before carcinomatosis	0.75 [0.16 ; 3.49]	0.717[5]
Differentiated adenocarcinoma	1.28 [0.39 ; 4.18]	0.688[5]
Peritoneal carcinomatosis (Metachrone)	1.69 [0.52 ; 5.54]	0.386[5]
Time between Carcinomatosis and primary tumor diagnosis ≥ 3 months	1.69 [0.52 ; 5.55]	0.386[5]

Hazard-Ratio (HR) [95% Confidence Interval], Univariate Cox model [5]

eTable 4. Multivariate analysis

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio	p-value	Hazard Ratio	p-value
PIPAC_CHEM group	0.141 [0.018 ; 1.105]	0.062[5]	0.141 [0.018 ; 1.104]	0.062[5]
WHO Performance Status	1.928 [0.746 ; 4.981]	0.175[5]	1.953 [0.690 ; 5.525]	0.207[5]

Hazard-Ratio (HR) [95% Confidence Interval], multivariate Cox models [5]

eTable 5. Median overall survival

	Whole study Population n =46	PIPAC_CHEM n =17	ONLY_CHEM n =29	p-value
Median overall survival (Months)	10.2 [7.3-12]	12.8 [7.2-34.3]	9.1 [5.4-11.5]	0.056[1]

Median Survival [95% Confidence Interval] – Log-Rank test [1]

6. Coûts d’hospitalisation pour chimiothérapie intrapéritonéale pulvérisée par aérosols

Nos deux premières études ont montré que la PIPAC procure un bénéfice de survie dans le traitement des CP. Cet acte relativement récent est pratiqué dans un petit nombre de centres en France et ne dispose pas encore de codage dans la classification commune des actes médicaux (CCAM). A notre connaissance, aucune étude évaluant les coûts de ce traitement pour les hôpitaux français n'a été menée et peu de données économiques sont disponibles sur les coûts de cette chimiothérapie.

L’objectif de cette évaluation économique a été d'estimer le coût moyen d’une hospitalisation pour PIPAC, dans un CHU et un Hôpital d’Instruction des Armées (HIA) français.

RESUME

Introduction : La PIPAC est une nouvelle technique chirurgicale pour le traitement de la carcinose péritonéale non résécable. Très peu de données sont disponibles sur les coûts de ce traitement en France, car il n'existe actuellement aucun codage PIPAC dans la Classification Commune des Actes Médicaux. Notre objectif était d'estimer le coût moyen d'hospitalisation pour PIPAC dans deux hôpitaux français.

Méthode : Le coût moyen d'une hospitalisation a été estimé à partir de la moyenne des rémunérations forfaitaires versées à l'hôpital et des surcoûts moyens de soins payés par l'établissement. A la sortie, l'hospitalisation d'un patient est classée dans un groupe lié au diagnostic, qui détermine la rémunération forfaitaire versée à l'hôpital (obtenue à partir de données du programme de médicalisation du système d'information – PMSI-MCO). Les coûts des dispositifs médicaux et des traitements médicamenteux spécifiques à la PIPAC, non couverts par la rémunération forfaitaire, ont été obtenus auprès des pharmacies hospitalières.

Résultats : Entre juillet 2016 et novembre 2021, 205 procédures PIPAC ont été réalisées chez 79 patients (moyenne des procédures par patient = 2,6). L'occupation moyenne du bloc opératoire était de 165 minutes. La rémunération forfaitaire moyenne perçue par les hôpitaux par hospitalisation PIPAC est de 4 031 €. Le coût moyen réel par hospitalisation était de 6 562 € pour une durée moyenne de séjour de 3,3 jours. Ainsi, chaque hospitalisation PIPAC a coûté en moyenne 2 531 € à l'hôpital.

Conclusion : Le remboursement actuel du traitement PIPAC par le système national de santé est insuffisant et ne représente que 61 % du coût réel engendré pour l'hôpital. La création d'un codage PIPAC dans la classification commune des actes médicaux prenant en compte cette différence de coût s'impose d'urgence afin de rendre ce traitement accessible à tous les patients éligibles.

European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Hospitalization cost of Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC)

Fatah Tidadini [a, b], Anne-Cecile Ezanno [c], Bertrand Trilling [a], Adeline Aime [c], Julio Abba [a], Jean-Louis Quesada [f], Alison Foote [a], Thierry Chevallier [d, e], Olivier Glehen [b], Jean-Luc Faucheron [a], Sihame Chkair [d, e], Catherine Arvieux [a, b, c, *]

[a] Department of Digestive and Emergency Surgery, Grenoble Alpes University Hospital, Grenoble, France
[b] Lyon Center for Innovation in Cancer, EA 3738, Lyon 1 University, Lyon, France
[c] Department of Visceral and Endocrine Surgery, Bégin Army Teaching Hospital, Saint-Mande, France
[d] Department of Biostatistics, Clinical Epidemiology, Public Health and Innovation in Methodology (BESPIM), CHU Nîmes, Univ Montpellier, Nîmes, France
[e] IDESP, UMR-INSERM, Montpellier, France
[f] Clinical Pharmacology Unit, INSERM CIC1406, Grenoble Alpes University Hospital, Grenoble, France

ARTICLE INFO

Article history:
Received 8 June 2022
Received in revised form
21 July 2022
Accepted 31 July 2022
Available online xxx

Keywords:
Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
Peritoneal carcinomatosis
Hospitalization costs

ABSTRACT

Introduction: Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC) is a new surgical technique for the treatment of unresectable peritoneal carcinomatosis. Very little data is available on the costs of this treatment in France as there is currently no code for PIPAC in the French Common Classification of Medical Acts (CCAM). Our objective was to estimate the mean cost of hospitalization for PIPAC in two French public teaching hospitals.

Methods: The mean cost of hospitalization was estimated from the mean fixed-rate remuneration paid to the hospital and the mean additional costs of treatment paid by the hospital. At discharge a patient's hospitalization is classified into a diagnosis related group, which determines the fixed-rate remuneration paid to the hospital (obtained from the national hospitals database - PMSI). Costs of medical devices and drug treatments specific to PIPAC, not covered by the fixed-rate remuneration, were obtained from the hospital pharmacies.

Results: Between July 2016 and November 2021, 205 PIPAC procedures were performed on 79 patients (mean procedures per patient = 2.6). Mean operating room occupancy was 165 min. The mean fixed-rate remuneration received by the hospitals per PIPAC hospitalization was €4031. The actual mean cost per hospitalization was €6562 for a mean length-of-stay of 3.3 days. Thus, each PIPAC hospitalization cost the hospital €2531 on average.

Conclusion: The current reimbursement of PIPAC treatment by the national health system is insufficient and represents only 61% of the real cost. The creation of a new fixed-rate remuneration for PIPAC taking into account this cost differential is necessary.

1. Introduction

Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC) is a new surgical technique developed for the treatment of initially unresectable peritoneal carcinomatosis (PC). This strategy, first described in 2012 by the group of Pr Marc-André Reymond, consists of applying chemotherapy agents directly to the peritoneum using a pressurized aerosol [1]. This treatment, carried out under general anesthesia, combines comprehensive laparoscopic exploration of the abdomen, an assessment of the peritoneal cancer index (PCI), peritoneal biopsies, and cytology (in the presence of ascites) before the administration of chemotherapy sprayed directly into the abdomen during a laparoscopy. A PIPAC procedure is performed every 6–8 weeks, alternating with systemic chemotherapy; replacing one cycle of intravenous chemotherapy with PIPAC. The justification for PIPAC is that it provides a better yield and drug

* Corresponding author. Department of Surgery, CHU Grenoble-Alpes, CS 10232, 38043, GRENOBLE CEDEX 09, France.
E-mail address: carvieux@chu-grenoble.fr (C. Arvieux).

https://doi.org/10.1016/j.ejso.2022.07.024
0748-7983/

Please cite this article as: F. Tidadini, A.-C. Ezanno, B. Trilling *et al.*, Hospitalization cost of Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC), European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2022.07.024

Abbreviations

PMSI	Programme de Médicalisation des Systèmes d'Information
FNHD	French National Hospitals Database
CCAM	French procedure coding system
GHM	Groupe homogène de malade
DRG	diagnosis related group,
GHS	Groupe homogène de séjours/homogeneous hospital stay groups
RSS	Résumé de sortie standardisé
UHSDA	Uniform hospital standardized discharge abstract
QALY	Quality-Adjusted Life-Year
PC	Peritoneal carcinomatosis

distribution to peritoneal tissue than hyperthermic intra-peritoneal chemotherapy (HIPEC) or intravenous chemotherapy, when comparing dose and tissular drug uptake [2]. The drug dose administered by PIPAC is seven to ten times less than that used intravenously, which limits adverse effects of the chemotherapy.

PIPAC has been applied to PC of all origins [3–10], and performed in more than 39 countries worldwide [11]. Several recent studies have provided evidence that a therapeutic regimen combining PIPAC and systemic chemotherapy provides improved survival in the treatment of PC, without altering quality of life (QOL), even improving it [3,4,12–17]. It can also reduce the volume of the PC allowing it to become resectable and therefore accessible to complete excision surgery [18].

As PIPAC is a relatively new procedure, performed in a small number of centers in France, it does not yet have a specific code in the French Procedure Coding System (Common Classification of Medical Acts - CCAM). To our knowledge no study has been conducted evaluating the costs to French hospitals of this treatment and little economic data are available on the costs of this chemotherapy. In the United Kingdom, a cost-effectiveness study [19] has been conducted using a Markov model. The incremental cost-effectiveness ratio (ICER) was estimated as £31 868 per quality-adjusted life-year (QALY) gained for initial treatment in the baseline scenario analysis, thus positioning the intervention as the dominant strategy. This pioneering study in this indication drew on numerous sources of information including NHS databases, industry, the British National Formulary, as well as the literature [19].

In order to assess the cost of PIPAC treatment, we analyzed data from 205 PIPAC procedures performed in 79 patients with PC of all etiologies at the Grenoble Alpes University Hospital (CHU_GA) and at the Bégin army teaching hospital (HIA_B). The objective of this medico-economic assessment was to estimate the mean cost of hospitalization for patients undergoing PIPAC treatment, based on the mean fixed-rate remuneration received by the hospital and the cost of the treatment (medical devices and drugs) purchased by the hospital, and to compare them it to the fixed-rate payments received by the two establishments.

2. Methods

This study is an analysis of data extracted from the French National Hospitals Database (FNHD) [Programme de Médicalisation des Systèmes d'Information – PMSI]. The reference codes of all hospitalizations for PIPAC at the CHU-GA and HIA_B, between July 2016 and November 2021 were submitted to the FNHD. The following data were requested: Diagnosis-Related Group (DRG) [groupe homogène de malade – GHM], admission and discharge date, total length-of-stay, the rate charged (homogeneous hospital stay group -GHS), basic GHS (without any supplements), total valuation of GHS (with any supplements), list of acts performed and total duration of occupation of the operating room.

As part of the French National Hospitals Database developed in the fields of medicine, surgery and obstetrics (PMSI-MCO), a uniform hospital standardized discharge abstract (RSS) is completed for each hospitalization (care during stays and procedures). It includes administrative data relating to the patient and the stay and medical data, diagnoses and procedures coded according to imposed classifications. The RSSs are then classified into a deliberately limited number of coherent groups, from a medical and costing point of view, the DRGs.

Within each DRG root, there are four levels of severity (level 1: without severity, levels 2, 3 and 4: with increasing severity). These levels depend on the severity of the clinical case, which is determined by the associated diagnoses called AC (associated comorbidities).

In brief, the cost of a hospitalization for PIPAC includes the cost of the surgery itself, the laboratory analyses and the cost of the hospital stay. PIPAC is carried out in an operating room and comprises exploratory laparoscopy (code ZCQC002) and intraperitoneal administration of pharmacological anticancer agent(s) under general anesthesia (code HPLB003). The analyses include the histopathological examination of staged biopsies (code ZZQX077) and cytopathological examination of the smear of a sample or several undifferentiated samples (code ZZQX128). The cost of the hospital stay associated with this intervention includes expenses related to imaging, treatments, biological laboratory analyses, stays in intensive care, etc.. In addition to these procedures, PIPAC requires medical devices (MDs - often single-use equipment) and expensive drug treatments that have to be purchased by the hospital.

The "conventional" acts carried out in the operating room associated with the principal diagnosis (PD) of the patient ultimately give rise to the hospital receiving a fixed-rate remuneration (GHS) that depends on how the hospitalization is classified (DRG). However, the cost of the specialized MDs needed for the PIPAC procedure, and the expensive intraperitoneal chemotherapy products and their preparation are not covered by this payment and are therefore financed by the hospital.

The assessment of the mean cost of a PIPAC hospitalization was estimated as the sum billed to the health insurance system using the official 2021 French rates expressed in euros. Treatments specific to PIPAC therapy, not included in the fixed-rate renumeration and de facto paid for by the hospital, were estimated based on the unit purchase costs (including tax) in euros in 2021.

2.1. PIPAC surgical procedure

All surgeons involved in PIPAC procedures have completed PIPAC training [11]. Procedures are performed in a dedicated operating room with a team of specialist operating-room nurses assigned to PIPAC procedures. A safety checklist before the intervention by the surgeons, the operating-room nurses and the pharmacist) is used at the three different stages of each procedure.

PIPAC procedures are performed as previously described [1,20]. Briefly, under general anesthesia, an open laparoscopic technique is used so as to prevent intestinal wounds, which would contraindicate the procedure. A 12 mmHg pneumoperitoneum is created, and to ensure safety the pressure in the pneumoperitoneum is kept constant throughout the procedure. Three laparoscopic balloon trocars (of 5, 11 and 12 mm) are used. A thorough exploration of the abdomen, PCI assessment, peritoneal biopsies, and ascites cytology (in the case of ascites) are performed prior to administration of the chemotherapy aerosol.

The precise drug administration protocol is established in consultation with the specialist hospital pharmacist. In the CHU_GA center, for carcinomas of all origins, doxurubicin at a dose of 1.5 mg/m^2 is administered in combination with cisplatin at 7.5 mg/m^2 diluted in 40 and 150 mL of 0.9% sodium chloride, respectively. In the case of a contraindication to doxorubicin/cisplatin, oxaliplatin at a dose of 92 mg/m^2 in a 5% dextrose solution is recommended.

In the HIA_B center, doxurubicin at a dose of 2.1 mg/m^2 is administered in combination with cisplatin at 10.5 mg/m^2 diluted in 40 and 150 mL of 0.9% sodium chloride, respectively. In the case of a contraindication, oxaliplatin at a dose of 92 mg/m^2 in a 5% dextrose solution is recommended.

A CE certified CAPNOPEN® nebulizer (Reger Medizintechnik GmbH, Villingendorf, Germany) connected to a high-pressure injector is inserted through the trocars. Nebulization of the drug is initiated remotely after all staff had left the operating room. The treatment is nebulized at 30 mL/min with a maximum pressure of 20 bars over 5 min. After 30 min of application, CO_2 and remaining toxic aerosols are evacuated through a closed-air evacuation system. The safety checklist is systematically verified, and signed by the surgeon in charge and the operating-room nurse.

Table 1
Breakdown by diagnosis related group (DRG) classification for PIPAC hospitalizations.

DRG code	GHS	Description	Fixed rate remuneration (euros)	Number of hospitalizations (%)
17C071	6331	CMD17 Intermediate interventions, level 1	3596.52	89 (43.4%)
17C061	6327	CMD17 Major Interventions, level 1	6069.96	5 (2.4%)
17C081	6335	CMD17 Minor Interventions, level 1	1466.29	5 (2.4%)
07C061	2319	Diagnostic interventions on the hepato-biliary and pancreatic system for malignancies, level 1	3905.73	2 (1%)
23C021	7901	Surgical interventions with other reasons for use of health services, level 1	1378.62	2 (1%)
06C211	2000	Other procedures on the digestive tract by laparotomy, level 1	3753.63	1 (0.5%)
16M091	6172	Other disorders of the reticuloendothelial or immune system, level 1	1345.11	1 (0.5%)
06C151	1983	Interventions on the digestive tract apart from laparotomies, level 2	2600.84	43 (21%)
06C152	1984	Other interventions on the digestive tract apart from laparotomies, level 2	4545.73	29 (14.2%)
17C072	6332	CMD17 Intermediate interventions, level 2	5422.01	4 (2%)
06C212	2001	Other interventions on the digestive tract by laparotomy, level 2	6304.93	1 (0.5%)
07C062	2320	Diagnostic interventions for malignancies on the hepato-biliary and pancreatic system, level 2	7651.81	1 (0.5%)
17C062	6328	CMD17 major interventions, level 2	8618.67	1 (0.5%)
17C082	6336	CMD17 minor interventions, level 2	4792.86	1 (0.5%)
23C022	7902	Surgical interventions with other reasons for use of health services, level 2	5640.02	1 (0.5%)
06C153	1985	Other interventions on the digestive tract apart from laparotomies, level 3	6752.52	7 (3.4%)
17C073	6333	CMD17 Intermediate interventions, level 3	10 412.77	4 (2%)
06C213	2002	Other interventions on the digestive tract by laparotomy, level 3	8839.96	1 (0.5%)
13C093	4951	Diagnostic laparoscopy or coelioscopy, level 3	6670.46	1 (0.5%)
06C133	1976	Release of peritoneal adhesions, level 3	6954.49	1 (0.5%)
17C083	6337	CMD17 minor interventions, level 3	10 563.22	1 (0.5%)
06C214	2003	Other interventions on the digestive tract by laparotomy, level 4	16 000.39	1 (0.5%)
06C044	1942	Major interventions on the small bowel and colon, level 4	15 419.86	1 (0.5%)
23Z02Z	7994	Palliative care, with or without an act	6051.88	1 (0.5%)
28Z07Z	9606	Chemotherapy for tumor, in sessions	384.02	1 (0.5%)

CMD17: Major Diagnostic Category No. 17 (includes malignant hematological conditions, benign or malignant tumors of vague or diffuse site and history of malignant tumors).

Table 2
–Characteristics of hospitalizations for PIPAC.

	Total Population (n = 205)	CHU_ GA (n = 98)	HIA_B (n = 107)	P value
Length of stay (days)	3.3 ± 3.4 (0–35) 2 [2; 3]	4.3 ± 4.6 (0–35) 3 [2; 4]	2.4 ± 1 (1–10) 2 [2; 3]	≤0.001 [a]
Length of stay in ICU (days)	5.5 ± 4.9 5.5 [2; 9] n = 2	– 2 n = 1	– 9 n = 1	–
Total time of operating room occupancy (min)	165.2 ± 37.8 (106–313) 157 [139; 185]	187.4 ± 41 (106–313) 183.5 [159; 205]	144.9 ± 18.4 (110–203) 140 [133; 159]	≤0.001 [a]
Mean number of procedures	4.7 ± 2.3 (1–14) 4 [3; 6]	5.8 ± 2.2 (2–14) 5 [4; 7]	3.7 ± 1.8 (1–11) 3 [3; 5]	≤0.001 [a]
Type of PIPAC treatment				
Doxorubicin + Cisplatin	145 (70.7%)	55 (56.1%)	90 (84.2%)	≤0.001 [b]
Oxaliplatin	60 (29.3%)	43 (43.9%)	17 (15.8%)	
Number of PIPAC procedures per patient	2.6 ± 2 (1–11) 2 [1; 3]	2 ± 1.1 (1–6) 2 [1; 3]	3.5 ± 2.7 (1–11) 3 [1; 5]	0.021 [a]

Median [25th; 75th percentiles] (min-max); Number(percentage).
[a] Mann-Whitney test.
[b] Chi square test.

2.2. Statistical analysis

Continuous data are presented using descriptive statistics (mean ± Standard-Deviation or median [25th; 75th percentiles]). Categorical data are presented using frequencies and percentages. Quantitative parameters were compared between groups using the Student *t*-test, or Mann-Whitney test when normality was rejected. Qualitative parameters were compared between groups using the Chi-square test or Fisher exact test, as appropriate. A threshold of 5% was used to define the significance of the statistical tests. Statistical analysis was performed using Stata software version 14.2 (STATA, StataCorp, Texas, USA).

3. Results

3.1. Attribution of a homogeneous hospital stay group to each hospitalization

Between July 2016 and November 2021, 205 hospitalizations for PIPAC, concerning 79 patients, were recorded (98 procedures on 48 patients at the CHU_GA and 107 procedures on 31 patients at the HIA_B). As there is no code for PIPAC these hospitalizations were classified by the hospital administrations into 25 different homogeneous hospital stay groups (GHS) (Table 1).

3.2. Length of hospital stay

The mean length of stay was 3.3 days. Patients treated at the HIA-B center had a shorter mean total length of stay compared to patients treated at the CHU_GA (mean 2.4 vs 4.3 days; p = ≤0.001) (Table 2). Fig. 1a shows the distribution of the total length of hospital stay for the 205 hospitalizations.

3.3. Acts performed during PIPAC procedures

For the 205 PIPAC procedures performed, a total of 872 acts were attributed a PMSI code, with a mean of 4.7 acts per procedure (min: 1 and max: 14). PIPAC procedures at the HIA_B were attributed fewer coded acts than those at the CHU_GA (mean 3.7 vs. 5.8 acts; p = ≤0.001) (Tables 2 and 3).

3.4. Operating room occupancy

The mean operating room occupancy time was 165.2 min. Patients treated at the HIA_B center spent less time in the operating room compared to those at the CHU_GA (mean 144.9 vs 187.4 min p − ≤0.001) (Table 2). The distribution of operating room occupancy is shown in Fig. 1b.

3.5. Fixed-rate remuneration per hospitalization received by the two hospitals

The mean remuneration received by the hospitals for a hospitalization for PIPAC was €4031. The CHU_GA and HIA_B received €4476 and €3623 per hospitalization, respectively (Table 4). Fig. 1c shows the distribution of the fixed-rate remuneration received for the 205 hospitalizations.

3.6. Real mean cost of hospitalization for PIPAC

The mean cost of the devices and treatments consumed during a PIPAC procedure was estimated from the exhaustive list of all the resources required during the procedure at each of the two centers. It amounted to €2485.64 for medical devices and €45.04 for drugs.

At the CHU_GA the difference was €2554 per PIPAC, i.e. €250,292 for 98 procedures. While at the HIA_B, the difference was €2507 per PIPAC performed, €268,249 for 107 procedures.

In total, the mean real cost of hospitalization including the cost of devices and treatments consumed for PIPAC is estimated at €6562 for the entire study population, €7030 at CHU_GA and €6130 at HIA_B. The difference between the fixed remuneration received by the two hospitals per hospitalization and the actual cost of the hospitalization for PIPAC was €2531 per PIPAC procedure, i.e. €518,855 for 205 procedures, an annual additional cost

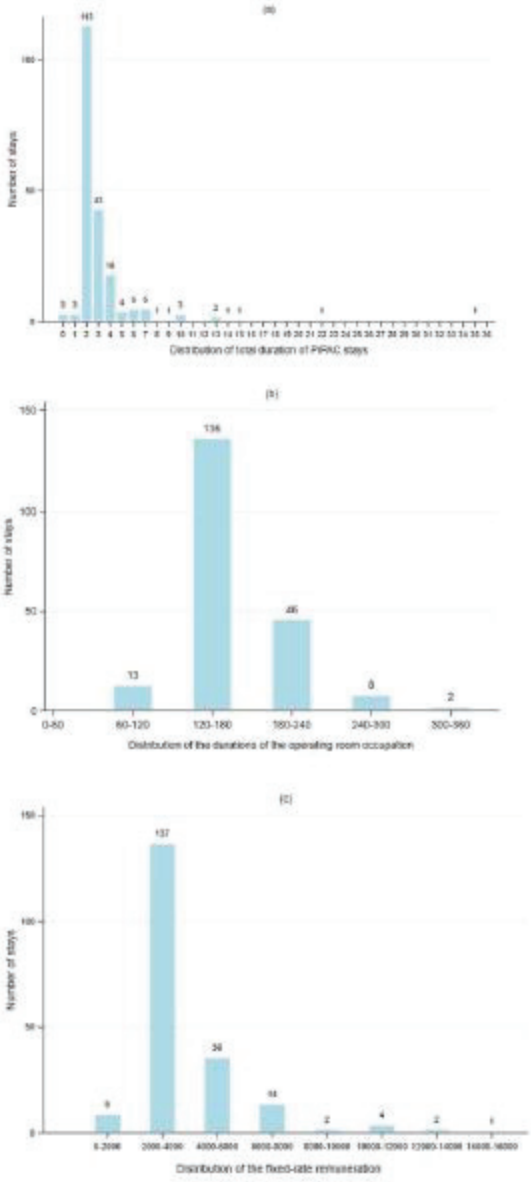


Fig. 1. (a) Distribution of the total lengths of the 205 hospital stays. (b) Distribution of the durations of occupation of the operating room for 205 PIPACs. (C) Distribution of the fixed-rate remuneration received for PIPAC hospitalizations.

Table 3
Acts performed during a PIPAC procedure.

CODE	Description	Total number of procedures (n = 205)	CHU-GA (n = 98)	HIA_B (n = 107)
ZCQC002	Exploration of the abdominal cavity by coelioscopy [Exploratory coelioscopy]	200	93	107
HPFC001	Excision of a peritoneal fold lesion [meso] without intestinal resection, by coelioscopy	170	81	89
HPLB003	Session of intraperitoneal injection of a pharmacological anticancer agent, under general anesthesia*	97	97	0
HPLB002	Session of intraperitoneal injection of a pharmacological anticancer agent, by transcutaneous route	92	0	92
ZZQX162	Histopathological examination of biopsy of an anatomical structure	51	40	11
ZZQX128	Cytopathological examination of the smear of a sample or several undifferentiated samples of fluid from an anatomical structure	48	36	12
ZCJC001	Evacuation of intra-abdominal fluid collection, by coelioscopy or by retroperitoneoscopy	32	32	0
ZZQX077	Histopathological examination of staged biopsies of an anatomical structure	24	9	15
ZZQX069	Immunocytochemical or immunohistochemical examination of cell or tissue sample fixed with 1–2 antibodies, without signal quantification of signal quantification	24	15	9
HPQX005	Anatomo-histopathological examination for oncological purposes of excision specimen of tumor of the greater omentun, peritoneum and/or peritoneal fold [meso]	22	16	6
ZZQX027	Immunocytochemical or immunohistochemical examination of cell or tissue samples fixed with 3–5 antibodies, without signal quantification	19	13	6
ZZQX188	Anatomo-histopathological examination of excision sample in one piece or of undifferentiated fragments, of an anatomical structure	18	17	1
ZZQX116	Cytopathological examination of cell pellet of a sample or of several undifferentiated samples of liquid and/or puncture product of anatomical structure, with paraffin fixation	14	12	2
ZZQX034	Immunocytochemical or immunohistochemical examination of cell or tissue sample fixed with 6–9 antibodies, without signal quantification	11	4	7
HPFA003	Excision of lesion of a peritoneal fold [meso] without intestinal resection, by laparotomy	9	9	0
ZZQX149	Extemporaneous cytopathological and/or histopathological examination of a sample of anatomical structure, outside the site of the sampling	5	5	0
ZCQA001	Exploration of the abdominal cavity by laparotomy [Exploratory laparotomy]	5	5	0
ZZQX127	Anatomo-histopathological examination of excision specimen of differentiated fragments of an anatomical structure	3	1	2
ZZQX180	Anatomo-histopathological examination of excision specimen of 2 anatomical structures	3	3	0
ZZQX092	Immunocytochemical or immunohistochemical examination of fixed cell or tissue sample, with 10 or more antibodies, without quantification of signal	3	3	0
HPPC003	Section of band and/or peritoneal adhesions for acute intestinal occlusion, by coelioscopy	3	3	0
ZZQX081	Immunocytochemical or immunohistochemical examination of a cell or tissue sample fixed with 1–2 antibodies, with quantification of the signal for each antibody	2	0	2
ZZLP900	Session of intra-arterial locoregional administration of anticancer pharmacological agent by an implanted device, without CEC, without hyperthermia	2	0	2
ZZQX045	Immunocytochemical or immunohistochemical examination of cell or tissue sample fixed with 3–5 antibodies, with signal quantification for each antibody	2	2	0
ZZQX163	Histopathological examination of biopsy of 2 anatomical structures	2	1	1
QZQX004	Anatomo-histopathological examination for oncological purposes of a piece of excision of skin and/or suprafascial [susaponeurotic] soft tissue of less than 5 cm^2	1	1	0
QZQX005	Anatomo-histopathological examination for oncological purposes of a piece of excision of skin and/or suprafascial [susaponeurotic] soft tissue of 5 cm^2 lor more	1	1	0
HGCC026	Cutaneous enterostomy, by coelioscopy	1	1	0
ZZQX175	Extemporaneous cytopathological and/or histopathological examination of 2–4 differentiated samples of an anatomical structure, outside the site of sampling	1	1	0
ZCIA004	Evacuation of several intra-abdominal fluid collections, by laparotomy	1	1	0
HGCA002	Suture of wound or perforation of the small intestine, by laparotomy	1	1	0
ZZQX058	Cytopathological or histopathological examination by in situ hybridization, with signal quantification	1	1	0
HPNC001	Destruction and/or excision of superficial endometriotic lesion of the peritoneum, by coelioscopy	1	1	0
ZZQX151	Cytopathological examination of the smear of a sample or several undifferentiated samples of an anatomical structure puncture product	1	0	1
ZZQX119	Extemporaneous cytopathological and/or histopathological examination of a sample of an anatomical structure, at the site of sampling	1	1	0
ZZHA001	Intraoperative sampling for cytological and/or extemporaneous anatomo-histopathological examination	1	0	1
Total		872	506	366

Act coded HPLB003 at CHU_GA and HPLB002 at HIA_B, without impacting the amount of GHS. Number.

of €103,771 (Table 4).

The current French National Hospitals Database (PMSI) valuation of hospitalization for a PIPAC treatment represents only 61% of the overall cost to the hospital.

4. Discussion

For two French public teaching hospitals, we estimated the mean cost to the hospital of PIPAC procedures. These estimates take into account the fixed rate remuneration received from the French healthcare system and the additional costs linked to PIPAC treatment paid by the establishment.

The mean remuneration received by the hospital was calculated for the whole hospitalization and took into account the costs of both the surgical intervention for PIPAC and the hospital stay associated with this procedure, at a fixed rate (GHS) determined by how the patient's hospitalization had been classified by the hospital administration (DRG) (Table 1). The length of hospital stay was significantly different between the two hospitals.

The cost of single-use medical devices, purchase of expensive drug treatments specific to the PIPAC surgical intervention, and their preparation, are not covered in by the fixed-rate remuneration. They are at the expense of the hospital.

The mean fixed-rate remuneration per hospitalization received

Table 4
Hospital costs.

Type of resource use	Total Population (n = 205)	CHU_ GA (n = 98)			HIA_B (n = 107)		
GHS valuation	Total Price (euros)	n	Price (euros)	Total Price (euros)	n	Price (euros)	Total Price (euros)
Mean valuation of a PIPAC hospitalization excluding expensive drugs and non considerated in the fixed rate remuneration	**4031 ± 1962 (383–15421)**			**4476 ± 2409 (383–15421)**			**3623 ± 1323 (1432–13210)**
Costs for PIPAC	Mean Price (with tax)	Quantity	Item Purchase price (with tax)	Total Price (with tax)	Quantity	Item Purchase price (with tax)	Total Price (with tax)
Disposable CAPNOPEN preparation kit		1	2160	2160	1	2160	2160
Slotted sterile brilliance amplifier C-arm cover		1	4.98	4.98	1	19.20	19.20
Tubular smoke evacuation system with valve		1	22.8	22.8	1	20.40	20.40
Tubular smoke evacuation system pipe endpiece size II		1	20.4	20.4	1	15.60	15.60
Viro safe smoke evacuation system filter		1	270	270	1	225	225
Disposable 200 ml medtron ELS syringe injector		1	6	6	2	6.24	12.48
Disposable medtron injector high pressure joint		1	7.2	7.2	1	5.66	5.66
Disposable medtron injector accutron HP-D Y valve		1	21.6	21.6	0	0.00	0
	2485.64			**2512.98**			**2458.3**
Treatments							
Oxaliplatin		0.44	13.15	6.44	0.17	14.57	12.65
Doxorubicin		0.56	0.24	0	0.83	7.15	0
Cisplatin		0.56	0.92	0	0.83	5.11	0
Preparation of drugs		1	35	35	1	36.00	36.00
	45.04			**41.44**			**48.65**
Total cost							
Real cost of PIPAC hospitalization including expensive drugs	**6562 ± 1962**			**7030 ± 2409**			**6130 ± 1323**
Difference borne by hospital per PIPAC hospitalization	**2531**			**2554**			**2507**
Difference borne by both hospitals for all PIPAC hospitalizations	**518 855**			**250 292**			**268 249**

Mean ± standard deviation (min-max).

by the hospitals was €4,031, while the mean real cost of hospitalization for PIPAC was €6562. The difference is borne by the hospitals and amounts to €2531 per PIPAC carried out, for an average stay of 3.3 days. At CHU_GA, this mean remuneration included the cost of the stay by one patient in a continuous care unit for 2 days. At the HIA_B it included hospitalization of one patient in intensive care for 9 days due to an immuno-allergic reaction to oxaliplatin.

In a study published in October 2021, comparing the results of PIPAC plus systemic chemotherapy with those of systemic chemotherapy alone in patients with gastric PC, we showed that PIPAC not only improves survival at 6 months from diagnosis of PC ($p = 0.0054$), but it also reduces the total duration of hospitalizations (PIPAC procedures and other readmissions included). This reduction in the total duration of hospitalization in the 6 months following the diagnosis of carcinomatosis, including the hospitalization necessary for each PIPAC procedure and/or session of non-ambulatory chemotherapy) has also been demonstrated in other studies [17]. PIPAC has usually low impact on QOL [12–14], severe complications post-PIPAC are not exceptional and do sometimes impact QOL. Indeed, PIPAC could even improve the outcome as of the 79 patients included in our analysis, 7 patients (8.8%) were able to benefit from R0 radical surgery after PIPAC (4 (8.3%) patients at the CHU_GA [21], and 3 (9.6%) at the HIA_B).

In a meta-analysis of 106 articles or case reports of PIPAC, summarizing 45 clinical studies of 1810 PIPAC procedures performed on 838 patients, Alyami et al. confirmed the feasibility, tolerance and safety of the PIPAC treatment [16]. In another study of 100 hospitalizations for PIPAC at the CHU_GA (of which 98 were included in the cost analysis), evaluating postoperative pain, pain at day 30 (D30), morbidity and mortality [22], we showed that PIPAC was well tolerated and that the intensity of pain was well controlled in the majority of patients. The intensity of pain was greatest at 4 p.m. on day zero (D0) and at 8 a.m. and 4 p.m. on day one (D1). The length of hospitalization was correlated with the level of post-operative pain. We also showed that the severe morbidity rate (Clavien–Dindo 3–4) in our study was comparable or slightly lower than that in the literature; three patients (6.1%) had died by day 30 (two due to major deterioration in their general condition and another following sepsis and an occlusive syndrome).

Given the clinical results, we think that the creation of an intermediate type of hospitalization in-between outpatient and conventional hospitalization, is necessary. This would imply admission on the day of the surgical intervention and discharge on D1 or D2, if the criteria for early discharge are met (Chung score >8) [23]. Thus reducing the length of hospitalization without increasing the risks for the patients. It should be noted that this approach has already been initiated at the HIA-B; in which the patients are discharged on postoperative D1 or D2 after more than 73% of procedures (77 discharged on D2 and the others on D1). During the period of inclusion of patients by this center, initially, patients were admitted the day before PIPAC. However, since the beginning of 2022 hospital admission has been done on the same day as surgery, with a check-up 48 h beforehand to validate the chemotherapy the day before PIPAC. This strategy has not caused any problems and even made it possible to streamline care. It is thus possible to shorten the duration of hospitalization. While at the CHU_GA, 40 discharges from hospital were recorded between 0 and 2 days, i.e. a rate of 40.8% (35 discharges on D2, 2 others on D1 and three PIPACs were even performed on an outpatient basis).

From a pharmacological perspective, oxaliplatin-based PIPACs were identified in our study as a risk factor associated with more post-operative pain than PIPAC with doxorubicin-cisplatin [22]. We recommend giving preference to doxorubicin-cisplatin based PIPACs as this combination allows better control of post-operative pain and therefore reduces the duration of hospitalization and the cost of treatment.

The length of hospitalization was significantly shorter at the HIA_B compared to at the CHU-GA (average 2.4 vs 4.3 days; $p = \leq 0.001$). The duration of hospitalization at CHU_GA being similar to that reported in the literature [24,25]. Operating room occupancy was also significantly shorter at the HIA_B (mean 144.9 min) than at the CHU-GA (187.4 min) ($p = \leq 0.001$). This is

probably not due to the duration of the procedure itself but to significant organizational differences between the two centers; in particular the transfer of patients between the intervention and recovery rooms. A factor that has an impact on our cost assessment was that patients treated at the HIA_B had fewer procedures coded than patients from CHU_GA (mean 3.7 vs 5.8 procedures; $p = <0.001$). This difference is due to the number of acts reported and not to the number of acts actually carried out, and is exacerbated by the fact there is no specific code for PIPAC.

These differences explain the differences in the fixed remuneration received (€4476 vs. €3623) and the actual costs of hospitalizations (€7030 vs. €6130) respectively.

The creation of a Procedure code (CCAM) for PIPAC that takes into account the difference between the fixed rate remuneration and the real cost would minimize differences from one establishment to another, reduce costs borne by the hospital, and simplify the reporting and coding of hospitalization for PIPAC for overstretched surgeons and administrative staff.

The main limitation of this study concerns incomplete data; both the surgeons and the hospital laboratories performed acts which were not systematically coded.

5. Conclusion

PIPAC is a palliative treatment, nevertheless, it can reduce the volume of the PC such that it becomes resectable and therefore accessible to complete excision surgery. Our study evaluated the hospitalization cost of this treatment over the first five years after its introduction at two French public sector teaching hospitals. The current French National Hospitals Database valuation of hospitalization for a PIPAC treatment is insufficient and accounts for only 61% of the overall cost to the hospital. The creation of a code for PIPAC in the French procedure coding system that takes into account this cost difference, is urgently needed so as to make this treatment accessible to all eligible patients.

Funding

No funding was received for conducting this study.

CRediT authorship contribution statement

Fatah Tidadini: Data curation, Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Anne-Cecile Ezanno:** Data curation, Investigation, Writing – review & editing. **Bertrand Trilling:** Data curation, Investigation. **Adeline Aime:** Data curation, Investigation. **Julio Abba:** Data curation, Investigation. **Jean-Louis Quesada:** Formal analysis, Writing – review & editing. **Alison Foote:** Writing – original draft, Writing – review & editing. **Thierry Chevallier:** Methodology. **Olivier Glehen:** Formal analysis, Writing – review & editing. **Jean-Luc Faucheron:** Data curation, Writing – review & editing. **Sihame Chkair:** Conceptualization, Methodology, Writing – review & editing. **Catherine Arvieux:** Data curation, Conceptualization, Investigation, Writing – review & editing.

Declaration of competing interest

None of the authors have a conflict of interest to declare.

References

[1] Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc 2012;26(7):1849–55. https://doi.org/10.1007/s00464-012-2148-0.

[2] Davigo A, Passot G, Vassal O, Bost M, Tavernier C, Decullier E, et al. PIPAC versus HIPEC: cisplatin spatial distribution and diffusion in a swine model. Int J Hyperther 2020;37(1):144–50. https://doi.org/10.1080/02656736.2019.1704891.

[3] Khomyakov V, Ryabov A, Ivanov A, Bolotina L, Utkina A, Volchenko N, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum 2016;1(3):159–66. https://doi.org/10.1515/pp-2016-0017.

[4] Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. J Gastrointest Surg 2016;20(2):367–73. https://doi.org/10.1007/s11605-015-2995-9.

[5] Tempfer CB, Celik I, Solass W, Buerkle B, Pabst U, Zieren J, et al. Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. Gynecol Oncol 2014;132(2):307–11. https://doi.org/10.1016/j.ygyno.2013.11.022.

[6] Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol 2015;137(2):223–8. https://doi.org/10.1016/j.ygyno.2015.02.009.

[7] Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Colorectal Dis 2016;18(4):364–71. https://doi.org/10.1111/codi.13130.

[8] Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clin Exp Metastasis 2017;34(5):309–14. https://doi.org/10.1007/s10585-017-9849-7.

[9] Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS One 2017;12(10):e0186709. https://doi.org/10.1371/journal.pone.0186709.

[10] Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C. First clinical data of pressurized intraperitoneal aerosol chemotherapy (PIPAC) as salvage therapy for peritoneal metastatic biliary tract cancer. Anticancer Res 2018;38(1):373–8. https://doi.org/10.21873/anticanres.12232.

[11] Alyami M, Sgarbura O, Khomyakov V, Horvath P, Vizzielli G, So J, et al. Standardizing training for pressurized intraperitoneal aerosol chemotherapy. Eur J Surg Oncol 2020;46(12):2270–5. https://doi.org/10.1016/j.ejso.2020.05.007.

[12] Somashekhar SP, Ashwin KR, Rauthan CA, Rohit KC. Randomized control trial comparing quality of life of patients with end-stage peritoneal metastasis treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) and intravenous chemotherapy. Pleura Peritoneum 2018;3(3):20180110. https://doi.org/10.1515/pp-2018-0110.

[13] Graversen M, Detlefsen S, Bjerregaard JK, Fristrup CW, Pfeiffer P, Mortensen MB. Prospective, single-center implementation and response evaluation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastasis. Ther Adv Med Oncol 2018;10:1758835918777036. https://doi.org/10.1177/1758835918777036.

[14] Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, et al. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Eur J Surg Oncol 2015;41(10):1379–85. https://doi.org/10.1016/j.ejso.2015.06.001.

[15] Alyami M, Bonnot PE, Mercier F, Laplace N, Villeneuve L, Passot G, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. Eur J Surg Oncol 2021;47(1):123–7. https://doi.org/10.1016/j.ejso.2020.05.021.

[16] Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol 2019;20(7):e368–77. https://doi.org/10.1016/S1470-2045(19)30318-3.

[17] Tidadini F, Abba J, Quesada JL, Baudrant M, Bonne A, Foote A, et al. Effect of pressurized intraperitoneal aerosol chemotherapy on the survival rate of patients with peritoneal carcinomatosis of gastric origin. J Gastrointest Cancer October 2021. https://doi.org/10.1007/s12029-021-00698-8.

[18] Kepenekian V, Péron J, You B, Bonnefoy I, Villeneuve L, Alyami M, et al. Non-resectable malignant peritoneal mesothelioma treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) plus systemic chemotherapy could lead to secondary complete cytoreductive surgery: a cohort study. Ann Surg Oncol 2022;29(3):2104–13. https://doi.org/10.1245/s10434-021-10983-2.

[19] Javanbakht M, Mashayekhi A, Branagan-Harris M, Horvath P, Königsrainer A, A Reymond M, et al. Cost-effectiveness analysis of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with gastric cancer and peritoneal metastasis. Eur J Surg Oncol 2022;48(1):188–96. https://doi.org/10.1016/j.ejso.2021.08.024.

[20] Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol 2014;21(2):553–9. https://doi.org/10.1245/s10434-013-3213-1.

[21] Tidadini F, Abba J, Quesada JL, Trilling B, Bonne A, Foote A, et al. Oncological outcomes after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in

the treatment of peritoneal carcinomatosis. J Gastrointest Cancer July 2022. https://doi.org/10.1007/s12029-022-00843-x.
[22] Tidadini F, Abba J, Quesada JL, Villeneuve L, Foote A, Baudrant M, et al. Assessment of postoperative pain after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the treatment of peritoneal metastasis. Int J Colorectal Dis May 2022. https://doi.org/10.1007/s00384-022-04182-y.
[23] Chung F, Chan VW, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 1995;7(6):500–6. https://doi.org/10.1016/0952-8180(95)00130-a.
[24] Hübner M, Teixeira Farinha H, Grass F, Wolfer A, Mathevet P, Hahnloser D, et al. Feasibility and safety of pressurized intraperitoneal aerosol chemotherapy for peritoneal carcinomatosis: a retrospective cohort study. Gastroenterol Res Pract 2017;2017:6852749. https://doi.org/10.1155/2017/6852749.
[25] Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol 2016;14:128. https://doi.org/10.1186/s12957-016-0892-7.

IV. DISCUSSION

IV.1. Partie 1 : Réhabilitation améliorée après chirurgie

Bien que le protocole RAC ait été développé il y a plusieurs années, et que de nombreuses études aient traité de ce thème, très peu d'études ont rapporté les bénéfices du programme en termes de résultats de la survie à long terme[50,51].

1. Effet de la réhabilitation améliorée et les facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer

Notre premier objectif a été d'étudier l'effet de la RAC et de déterminer les facteurs de risques sur la survie des patients à 3 ans. La SG a été comparée pour les patients traités selon les recommandations RAC par rapport au traitement conventionnel (pré-RAC).

Nos résultats ont montré que la SG à 3 ans après résection tumorale était significativement meilleure dans le groupe RAC que dans le groupe pré-RAC (p = 0,017), bien que les patients du groupe RAC aient statistiquement plus de comorbidités. L'analyse de la survie à 3 ans par un modèle de Cox multivarié a identifié le fait de recevoir le protocole RAC comme un facteur protecteur avec une réduction de 30 % du risque de décès par rapport au groupe pré-RAC, indépendamment des facteurs de confusion identifiés.

Le taux de survie à 3 ans dans le groupe RAC (76,1 %) était cohérent avec ceux rapportés dans la littérature, il y a un effet RAC sur la survie à 3 ans et 5 ans après résection colorectale pour cancer[50,51]. Les taux de survie à 1 an et à 3 ans de nos patients pré-RAC étaient respectivement de 86,6 % et 69,2 %. Nos résultats sont comparables à ceux rapportés par Launoy et al. dans une étude sur la survie des personnes atteintes d'un CCR en France métropolitaine entre 1989 et 201 8[55].

La durée totale du séjour hospitalier et le taux de réadmission à 90 jours étaient significativement plus courts dans le groupe RAC (p=≤0.001 et p = 0, 037), respectivement. Cependant, la durée de séjour dans notre étude était plus longue que celles rapportées dans la littérature[56–58]. Cela, peut s'expliquer par le déficit notoire des structures de soins de suite post-opératoire alternatives au retour à domicile dans la région grenobloise et qu'en France, les patients ou leur famille peuvent refuser une sortie alors qu'elle est préconisée par l'équipe médicale, pour des raisons diverses.

Notre étude a montré que la mise en place du protocole RAC est associée à une réduction de la durée d'hospitalisation et du taux de réadmission et une amélioration de la survie à 3 ans. La RAC est associée à une meilleure survie à 3 ans, indépendamment des autres paramètres couramment considérés. Un score ASA > 2, le tabagisme, des antécédents de cancer et de fibrillation auriculaire sont des facteurs de risque délétères liés à une mortalité précoce.

Sur le plan méthodologique, cette étude fait une comparaison historique entre 2 phases successives s'étalant sur une période de 13 ans. Il n'y avait donc pas de randomisation, ce qui constitue un risque de données manquantes et de biais de sélection[59]. En effet, au cours de ces 13 années, de nouvelles procédures ont été introduites ou améliorées, en plus des améliorations des traitements médicaux et des schémas thérapeutiques néo-adjuvants ou adjuvants. La prise en charge anesthésique, chirurgicale et globale a donc progressé en parallèle.

2. Association entre la réhabilitation améliorée, les facteurs de risque et la survie à 3 ans après chirurgie colorectale pour cancer chez les personnes âgées

Les essais cliniques en chirurgie cancérologique digestive sont généralement réalisés chez des patients adultes sélectionnés. Nous disposons de peu de données en ce qui concerne l'impact de la RAC sur la survie à moyen et long terme des patients âgés, ces derniers ayant été souvent exclus des essais cliniques[52]. Nous avons donc évalué le lien entre la mise en œuvre de ce programme et les facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer, spécifiquement chez la population âgée. Selon le groupe de collaboration sur le CCR, la définition des patients âgés est un âge supérieur ou égal à 65 ans et les patients ont été classés en 3 tranches d'âge : 65-74 ans, 75-84 ans et ≥ 85 ans[60].

Comme pour la population générale de notre série, les résultats de notre étude chez les patients âgés de 65 ans et plus ont montré, bien que les patients du groupe RAC aient statistiquement plus de comorbidités et de facteurs de risque, le taux de SG à 3 ans était significativement meilleur, quelle que soit la tranche d'âge par rapport au groupe pré-RAC (p=0,016). Notre étude a également montré que le taux de SG à 3 ans dépend de l'âge du patient (p ≤ 0,001). Ce résultat de la SG à 3 ans a été confirmé par une analyse du score de propension (HR = 0,67 [0,47-0,97], p = 0,032).

Plusieurs études ont rapporté que la RAC est non seulement réalisable chez les personnes âgées, mais les patients âgés bénéficient de ce programme après chirurgie colorectale autant que les patients plus jeunes[61], et que ce programme peut être appliqué en toute sécurité aux patients âgés pour réduire les complications et raccourcir la durée du séjour à l'hôpital[62]. Nos résultats vont dans le même sens que ceux de la littérature.

La durée totale d'hospitalisation était significativement plus courte dans le groupe RAC ($p \leq 0,001$). La durée de séjour des patients âgés de 65 ans et plus est quasiment la même que celle de la population générale pour les 2 groupes (médiane 11 [8-21] vs 15 days [11-25]) et (médiane 10 jours [7–19] vs 15 [10–23]) ; respectivement.

Nous avons montré que la mise en place de la RAC chez les patients âgés de notre service est associée à une meilleure survie à 3 ans après chirurgie du CCR, indépendamment des facteurs de risque. La tranche d'âge, le tabagisme, la fibrillation auriculaire et le score ASA > 2 sont des facteurs de risque délétères liés à la mortalité précoce. Les patients âgés de 65 ans et plus bénéficient donc autant de la RAC que les patients jeunes. Ce programme doit être indiqué pour tous les patients subissant une chirurgie colorectale, y compris ceux âgés de 65 ans et plus.

Cette étude est exposée aux mêmes biais de sélection que l'étude de la population générale. Nous avons essayé de corriger l'absence de randomisation par une analyse du score de propension, afin de tenir compte des différences dans les caractéristiques de base. Le score de propension a été réalisé sur 14 paramètres, identifiés comme facteurs de confusion.

3. Evaluation de la douleur post-opératoire après PIPAC dans le traitement de la carcinose péritonéale

Après avoir montré l'effet de la RAC sur l'évolution oncologique après résection colorectale pour cancer, nous nous sommes intéressés à l'impact de ce protocole sur la PIPAC, traitement de la CP, pathologie sévère, nécessitant une prise en charge et un environnement chirurgical particuliers.

Dans cette troisième étude, nous avons évalué la douleur post-opératoire incluant les données des 100 premières interventions PIPAC réalisées sur 49 patients atteints de CP toutes étiologies confondues et traités en mode RAC.

Notre évaluation a montré que la PIPAC est tolérée et que la douleur est bien contrôlée chez la majorité des patients. La douleur était maximale à 16h le jour d'intervention et à 8h et 16h à J1 post-opératoire. Sur le plan pharmacologique, la PIPAC à base d'Oxaliplatine est identifiée comme facteur de risque associé à plus de douleur post-opératoire comparativement aux PIPAC utilisant l'association Doxorubicine-Cisplatine, en analyse univariée, mais également en analyse multivariée, pour laquelle elle apparait comme un facteur délétère indépendamment du traitement aux opiacés. Cependant, nos résultats ne concordent pas avec la littérature après d'autres types de chirurgie[63–67] ; avec l'âge, le diabète, un score ASA élevé et le sexe féminin, sans lien significatif avec la douleur postopératoire. La douleur modérée à sévère est associée à des séjours hospitaliers plus longs.

Le traitement PIPAC peut être douloureux et que l'administration individualisée de morphine à la demande est parfois nécessaire pour contrôler la douleur. Ce mode de prise en charge souple a permis de contrôler la douleur chez la majorité de nos patients.

Ces résultats obtenus dans une étude rétrospective monocentrique démontrent une tolérance des procédures PIPAC à base de l'association Doxorubicine-Cisplatine, qui permettent de mieux contrôler la douleur post-opératoire et de réduire la durée d'hospitalisation.

Compte tenu de ces résultats cliniques et de la durée d'hospitalisation enregistrée, nous pensons que la création d'une hospitalisation intermédiaire entre l'ambulatoire et l'hospitalisation conventionnelle (RAC), avec entrée le jour de la PIPAC et une sortie à J1 ou J2 si les critères de sortie précoce sont remplis (évaluations clinico-biologiques et critère de CHUNG)[68], est peut-être à envisager pour ce traitement.

Sur le plan méthodologique, il est difficile d'étudier la douleur rétrospectivement car elle varie dans la journée en fonction de nombreux facteurs : mobilisation, transit digestif, appareillage par une sonde urinaire, une sonde gastrique ou un drainage, type d'antalgiques, posologie réellement prise par rapport à la prescription, etc. La mesure de l'EVA est un facteur crucial

d’appréciation qui peut aussi varier selon différents facteurs : mesure en continu ou par un certain nombre de mesures par jour, réalisé par un soignant, ou par le patient lui-même.

IV.1.1. Outils d’amélioration

Sur le plan méthodologique, nous avons mis en évidence le fait que les chirurgiens membres du groupe français de recherche en chirurgie du cancer rectal (GRECCAR) et les centres qui pratiquent déjà la PIPAC qui travaillent ensemble au sein du réseau RENAPE ont déjà bien implémenté la RAC dans leurs services. La randomisation entre RAC et traitement conventionnel (pré-RAC), selon les recommandations, nous parait peu acceptable par les équipes. Au vu des résultats encourageants du protocole RAC, il est en effet souvent considéré aujourd’hui comme contraire à l'éthique d'assigner des patients à un bras d'étude qui n'inclut pas la RAC. De ce fait, l’évaluation prospective, comparative et randomisée de l’impact de la RAC parait difficilement réalisable. Pour évaluer l’impact du programme à long terme, nous proposons plutôt de réaliser des études de cohortes prospectives et multicentriques, avec des analyses stratifiées et appariées selon des facteurs pronostiques connus et par score de propension.

IV.2. Partie 2 : Bénéfices et risques de la PIPAC

4. Résultats oncologiques de la chimiothérapie intrapéritonéale pulvérisée par aérosols dans le traitement de la carcinose péritonéale

Cette deuxième partie de travail avait pour objectif d’évaluer les bénéfices et risques de la PIPAC. Nous avons d’abord étudié les résultats oncologiques de nos 100 premières procédures PIPAC réalisées sur 49 patients atteints de CP, toutes étiologies confondues.

Sur les 28 patients ayant subi au moins deux interventions PIPAC, nous avons observé une régression ou au moins une stabilisation de la carcinose (au regard de score PCI) chez 18 patients (66,6 %), et une chirurgie radicale R0 avec HIPEC a été possible pour quatre d'entre eux. Les quatre patients étaient toujours en vie sans récidive à la date de l'analyse.

Après un temps de suivi médian de 16,1 mois (1,5-90,1), la SG médiane à partir du diagnostic de la CP était de 29,1 mois [14,8-34,3], avec une survie médiane de 11,3 [7,2-34,3] et

29,1 mois [16.1-31] ; respectivement pour les CP gastrique et colorectale. Nos résultats étaient conformes à la littérature[40, 46, 71]. Pour les CP d'autres origines, le nombre de cas était trop faible pour estimer la survie et établir une comparaison avec la littérature. L'analyse des sous-groupes selon le nombre de lignes de chimiothérapie systémique, les procédures PIPAC et le moment de l'apparition de la CP (synchrone ou métachrone) dans les populations gastriques et colorectales n'a pas entraîné de différence significative en termes de survie.

La SG après la première séance PIPAC était de 11,6 mois [6-17, 3], avec une survie médiane de 6 [2,9-15,5] pour les CP gastriques et 13,3 mois [5-17, 6] pour l'origine colorectale. La stratification des patients selon le nombre de lignes de chimiothérapie systémique, de procédures PIPAC et la chronologie d'apparition des CP (synchrone ou métachrone) chez les populations gastrique ou colorectale n'a pas abouti à une différence significative de survie.

La PIPAC administrée en alternance avec une chimiothérapie systémique semble retarder la progression oncologique par rapport à la chimiothérapie systémique seule et améliorer la survie[70–73].

Sur le plan méthodologique, notre étude fait une analyse des résultats oncologiques de patients atteints de CP toutes étiologies confondues. Il y avait donc un regroupement de patients très hétérogènes, ce qui constitue un risque de biais de représentativité des patients inclus dans l'analyse. Cependant, les résultats restent intéressants, car ils rendent compte de l'effet moyen du traitement PIPAC sur différents types de patients[74].

5. Effet de la chimiothérapie intrapéritonéale pulvérisée par aérosols sur le taux de survie des patients atteints de carcinoses péritonéales d'origine gastrique

Nous avons ensuite étudié l'effet de la PIPAC comparativement à une chimiothérapie systémique à 6 mois et sur l'ensemble du suivi de diagnostic d'une CP d'origine gastrique. Un groupe de patients avait bénéficié de la PIPAC administrée en alternance avec une chimiothérapie systémique et l'autre groupe était constitué de patients ayant été traités par une chimiothérapie systémique seule.

Dans cette étude rétrospective non randomisée, nous avons comparé la SG après deux stratégies de traitement pour des patients sélectionnés atteints d'un cancer gastrique de type

adénocarcinome et d'une CP non résécable. La stratégie de traitement de chaque patient avait été décidée par un comité multidisciplinaire. Les 46 patients inclus dans cette étude étaient tous éligibles au traitement PIPAC. Cependant compte tenu, du caractère innovant de la PIPAC, du manque de recul sur les éventuelles complications du traitement les premières années suivant son introduction (2016 à 2018) et afin d'éviter trois interventions sous anesthésie générale sur une période de 4 mois pour des patients âgés et fragiles, notre comité multidisciplinaire était plutôt réticent à une stratégie PIPAC chez les patients âgés. Ceci explique la différence d'âge entre les deux groupes.

Le traitement par PIPAC administré en alternance avec une chimiothérapie systémique a apporté une différence significative (p = 0,029) de SG à 6 mois après le diagnostic de la CP par rapport à la chimiothérapie systémique seule (94,1 % [65-99, 2] et 65,5 % [45,4 - 79,7] respectivement). Le nombre de jours d'hospitalisation, y compris ceux requis pour chaque procédure PIPAC et/ou séance de chimiothérapie non ambulatoire, à 6 mois était significativement inférieur dans le groupe PIPAC_CHEM (p = 0,045).

Après un suivi médian de 10,2 mois (0,4 ; 43,6) à compter du diagnostic de la CP, la survie médiane était plus longue dans le groupe PIPAC_CHEM (différence de 3,7 mois). PIPAC semble retarder la progression oncologique avec un effet significatif sur la survie à 6 mois qui semble se poursuivre pendant au moins 18 mois. Dans une méta-analyse de 106 articles ou rapports de cas de PIPAC, dont 45 études cliniques, Alyami et al.[46] ont rapporté une SG comprise entre 8 et 15 mois. Dans une étude plus récente, le même auteur rapporte une survie de 19,1 mois[75]. Ainsi, notre résultat semble être en accord avec la plupart des études publiées. Cependant, quelle que soit la stratégie thérapeutique, le pronostic à long terme reste sombre.

Sur le plan méthodologique, cette étude rétrospective, comparative et non randomisée était exposée à un risque de biais de sélection. Nous avons essayé de corriger l'absence de la randomisation par l'ajustement de comparaison de la survie à 6 mois entre les groupes, sur les facteurs de confusion identifiés. L'étude randomisée (EudraCT 2018-001035-40)[54] évalue actuellement en Allemagne, le bénéfice de la PIPAC chez les patients atteints de PC gastrique, fournira des informations plus fines sur l'effet de la PIPAC sur la SG dans cette indication.

6. Coûts d'une hospitalisation pour chimiothérapie intrapéritonéale pulvérisée par aérosols

Cette étude rétrospective avait pour objectif d'estimer le coût moyen pour l'hôpital des procédures PIPAC dans un CHU et un Hôpital d'Instruction des Armées (HIA) français. Ces estimations tiennent compte de la rémunération forfaitaire perçue par le système de santé français et des surcoûts liés au traitement PIPAC pris en charge par l'établissement.

La rémunération forfaitaire moyenne par hospitalisation perçue par les hôpitaux est de 4 031 €, tandis que le coût réel moyen d'hospitalisation pour la PIPAC est de 6 562 €. La différence est supportée par les hôpitaux et s'élève à 2 531 € par PIPAC réalisée, pour un séjour moyen de 3,3 jours. Cette rémunération moyenne incluait le coût des séjours en unité de soins continus et en réanimation.

Notre étude portait sur les PIPAC réalisées entre 2016 et 2021 pour traiter des CP de neuf origines différentes. Or, l'intervention et la prise en charge postopératoire sont parfois beaucoup plus lourdes pour certaines origines de CP par rapport à d'autres. La durée d'hospitalisation, l'occupation du bloc opératoire et le nombre d'actes étaient significativement différents entre les deux établissements. Ceci est probablement dû à des différences d'organisation importantes entre les deux centres et à l'origine de CP traitées. Ces écarts expliquent respectivement les différences de rémunération fixe perçue (4 476 € vs 3 623 €) et de frais réels d'hospitalisation (7 030 € vs 6 130 €).

Nos trois études sur la PIPAC dans le cadre de cette thèse, ont montré que la PIPAC améliore non seulement la survie à 6 mois du diagnostic de la CP (p = 0,005 4), mais réduit également la durée totale des hospitalisations, sans impact négatif sur la qualité de vie du patient, ce qui a été démontré également dans d'autres études[76]. Compte tenu de la gravité de la maladie, le recours à la thérapie PIPAC est donc une alternative permettant un réel bénéfice clinique, et donc de réduire la durée d'hospitalisation et le coût de la prise en charge.

Dans cette étude rétrospective, nous avons utilisé les données du PMSI et de la comptabilité analytique pour l'évaluation du coût moyen d'un séjour PIPAC et la méthode de « micro-costing » pour l'estimation du coût des dispositifs médicaux spécifiques au traitement PIPAC, les produits de chimiothérapie intrapéritonéale onéreux et la préparation. Ce couplage de

2 méthodes pourrait constituer un risque de biais pour la méthode de valorisation du coût réel de l'hospitalisation PIPAC.

IV. 2.1. Outils d'amélioration

Le contexte actuel est marqué par l'arrêt définitif des inclusions dans le cadre du seul essai clinique, prospectif, comparatif et randomisé, évaluant le traitement PIPAC en France, pour des patients atteints de CP d'origine gastrique (NCT04065139). Il nous parait actuellement donc non éthique de randomiser les patients entre PIPAC associée à de la chimiothérapie systémique à ceux de la chimiothérapie systémique seule.

- Pour les suivis à long terme, nous proposons de comparer de manière prospective et multicentrique deux cohortes de patients présentant une CP de même origine, traités par PIPAC associée à de la chimiothérapie systémique à ceux de la chimiothérapie systémique seule, dans le but de déterminer la SG à long terme. Pour effacer une partie des biais relatifs à l'absence de randomisation, nous procéderons à des analyses stratifiées et appariées selon les facteurs pronostiques connus.
- Pour l'évaluation économique, nous proposons de constituer une cohorte et évaluer le coût de l'ensemble du parcours de soins, du diagnostic de la carcinose jusqu'à guérison ou décès. Pour cela, nous proposons trois méthodes :

- Méthode de micro-costing.
- Collecte des données de l'ensemble du parcours dans un e-CRF.
- Interroger la sécurité sociale (CNAM) et récupérer le coût du parcours de soins via le système national de données de santé.

Enfin, nous avons noté au cours de nos travaux l'absence de données sur l'impact de ces deux stratégies innovantes (RAC et PIPAC) sur l'état psychologique des patients et/ou de leurs proches aidants, leur processus de réintégration sociale et leur qualité de vie. En effet, bien que ces paramètres soient évalués de façon plus ou moins formelle lors des consultations de suivi avec les chirurgiens, les données n'étaient pas collectées en dehors des essais cliniques, et n'ont pas pu être collectées rétrospectivement. Il serait donc nécessaire pour notre service de réaliser des études prospectives incluant cet aspect du suivi.

Tableau I : Principaux biais méthodologiques auxquelles nos études sont exposées et méthodes correctives.

Etudes	Biais/Limites	Méthodes correctives
Effet de la réhabilitation améliorée et facteurs de risque sur la survie à 3 ans après chirurgie colorectale pour cancer	Biais de sélection et risque de données manquantes	Ajustement de comparaison de la survie à 3 ans entre les groupes, sur les facteurs de confusion identifiés
Association entre la réhabilitation améliorée, les facteurs de risque et la survie à 3 ans après chirurgie colorectale pour cancer chez les personnes âgées	Biais de sélection et risque de données manquantes	Ajustement de comparaison de la survie à 3 ans entre les groupes, sur les facteurs de confusion identifiés Analyse par score de propension
Evaluation de la douleur post-opératoire après PIPAC dans le traitement de la carcinose péritonéale	Il est difficile d'étudier la douleur rétrospectivement car elle varie dans la journée en fonction de nombreux facteurs : mobilisation, transit digestif, appareillage par une sonde urinaire, une sonde gastrique ou un drainage, type d'antalgiques, posologie réellement prise par rapport à la prescription, etc. La mesure de l'EVA est un facteur crucial d'appréciation qui peut aussi varier selon différents facteurs : mesure en continu ou par un certain nombre de mesures par jour, réalisé par un soignant, ou par le patient lui-même	La méthode corrective serait de noter la quantité et la nature des antalgiques reçus par le patient, et retrouver en rétrospectif l'EVA de la douleur maximale dans la journée donnée par le patient
Résultats oncologiques de la chimiothérapie intrapéritonéale pulvérisée par aérosols dans le traitement de la carcinose péritonéale	Regroupement de patients très hétérogène, constitue un risque de biais de représentativité des patients inclus dans l'analyse	Aucune

Etudes	Biais/limites	Méthodes correctives
Effet de la chimiothérapie intrapéritonéale pulvérisée par aérosols sur le taux de survie des patients atteints de carcinoses péritonéales d'origine gastrique	Biais de sélection	Ajustement de comparaison de la survie à 6 mois entre les groupes, sur les facteurs de confusion identifiés
Coûts d'hospitalisation pour chimiothérapie intrapéritonéale pulvérisée par aérosols	Couplage de 2 méthodes pour la valorisation du coût réel de l'hospitalisation PIPAC	Aucune

V. CONCLUSIONS ET PERSPECTIVES

Les résultats que nous avons obtenus montrent l'impact de deux innovations stratégiques, la RAC et la PIPAC, sur la prise en charge des patients atteints d'un cancer digestif.

Nos travaux sur la RAC après chirurgie colorectale ont montré que cette pratique est efficace aussi bien chez les patients jeunes que chez les patients âgés de 65 ans et plus et que la mise en œuvre de ce programme dans notre service est associée à une meilleure survie à 3 ans, indépendamment des facteurs de risque. Le tabagisme, les antécédents de cancer, la fibrillation auriculaire, un score ASA> 2 et la tranche d'âge pour les patients âgés de 65 ans et plus sont des facteurs de risque délétères liés à une mortalité précoce.

Notre travail sur la RAC après PIPAC a montré que cette chimiothérapie est tolérée et la douleur post-opératoire est bien contrôlée chez la majorité des patients. Sur le plan pharmacologique, la PIPAC à base d'Oxaliplatine est identifiée comme facteur de risque associé à des douleurs post-opératoires plus intenses par rapport à celle à base de l'association Doxorubicine-Cisplatine. Sur le plan de l'organisation des soins, la création d'un type d'hospitalisation intermédiaire entre l'hospitalisation ambulatoire et l'hospitalisation conventionnelle (RAC) avec une admission le jour de l'intervention chirurgicale et une sortie à J1 ou J2, si les critères de sortie précoce sont remplis (score de Chung > 8)[68], nous parait une piste à envisager, car cela réduirait la durée d'hospitalisation sans augmenter les risques pour les patients.

Nos travaux sur les bénéfices et risques de la PIPAC ont montré une diminution de la progression oncologique, une amélioration de la survie par rapport à la chimiothérapie systémique sans PIPAC et une réduction de la durée totale des hospitalisations, sans impact négatif sur la qualité de vie du patient. Sur le plan économique, la valorisation de l'hospitalisation de 61 % seulement pour l'hôpital reste insuffisante par rapport au coût réel.

Nos travaux apportent de nouveaux éléments pouvant diminuer la morbi-mortalité et améliorer la qualité de vie des patients et de leurs proches aidants.

L'identification des biais méthodologiques permet de proposer des outils d'amélioration dans la mise en œuvre de futures études cliniques dans cette population. Pour évaluer l'impact du programme RAC et de la PIPAC à long terme, nous proposons de réaliser des études de

cohortes prospectives et multicentriques, avec des analyses stratifiées et appariées selon les facteurs pronostiques connus.

Sur le plan des perspectives, il parait nécessaire de confirmer l'effet de la RAC sur la survie à long terme après chirurgie colorectale pour cancer, en effectuant la même série études à 5 ans de l'intervention. Nous allons réaliser cette évaluation début 2023. Nos travaux sur la PIPAC ont été effectués dans un seul centre sur des petits effectifs hétérogènes : nous souhaitons les valider sur une cohorte plus importante et multicentrique. Enfin, nous soutenons la création d'un codage spécifique « PIPAC » dans la CCAM qui prendrait en compte le différentiel entre la rémunération forfaitaire et le coût réel, ce qui permettrait de minimiser les différences d'un établissement à l'autre, de réduire les coûts supportés par l'hôpital et de simplifier la déclaration et le codage.

VI. BIBLIOGRAPHIE

1. Cancer. Accessed July 5, 2022. https://www.who.int/news-room/fact-sheets/detail/cancer

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

3. Cancer du colon rectum. Accessed July 5, 2022. https://www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-colon-rectum

4. Seniors − France, portrait social | Insee. Accessed July 6, 2022. https://www.insee.fr/fr/statistiques/4238381?sommaire=4238781

5. Segelman J, Granath F, Holm T, Machado M, Mahteme H, Martling A. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. *Br J Surg*. 2012;99(5):699-705. doi:10.1002/bjs.8679

6. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422. doi:10.1093/annonc/mdw235

7. Sommariva A, Ansaloni L, Baiocchi GL, et al. Diagnostic and therapeutic algorithm for colorectal peritoneal metastases. A consensus of the peritoneal surface malignancies onco-team of the Italian society of surgical oncology. *Eur J Surg Oncol*. 2021;47(1):164-171. doi:10.1016/j.ejso.2020.09.035

8. Comprendre les cancers du côlon et du rectum. Accessed August 5, 2022. https://www.ameli.fr/assure/sante/themes/cancer-colorectal/comprendre-cancer-colorectal

9. Cancers du côlon : les points clés - Cancer du côlon. Accessed August 5, 2022. https://www.e-cancer.fr/Patients-et-proches/Les-cancers/Cancer-du-colon/Les-points-cles

10. Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for the management of colon cancer. *Dis Colon Rectum*. 2012;55(8):831-843. doi:10.1097/DCR.0b013e3182567e13

11. Monson JRT, Weiser MR, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). *Dis Colon Rectum*. 2013;56(5):535-550. doi:10.1097/DCR.0b013e31828cb66c

12. Cancers du côlon : les points clés - Cancer du côlon. Accessed October 7, 2022. https://www.e-cancer.fr/Patients-et-proches/Les-cancers/Cancer-du-colon/Les-points-cles

13. Cancers du rectum : la chirurgie - Cancer du rectum. Accessed October 7, 2022. https://www.e-cancer.fr/Patients-et-proches/Les-cancers/Cancer-du-rectum/La-chirurgie

14. Schilling PL, Dimick JB, Birkmeyer JD. Prioritizing quality improvement in general surgery. *J Am Coll Surg*. 2008;207(5):698-704. doi:10.1016/j.jamcollsurg.2008.06.138

15. Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. *Ann Surg*. 2015;261(3):497-505. doi:10.1097/SLA.0000000000000854

16. Patients âgés opérés et pris en charge pour un cancer colorectal : étude d'une cohorte monocentrique. Revue Medicale Suisse. Accessed July 5, 2022. https://www.revmed.ch/revue-medicale-suisse/2010/revue-medicale-suisse-250/patients-ages-operes-et-pris-en-charge-pour-un-cancer-colorectal-etude-d-une-cohorte-monocentrique

17. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer*. 2000;88(2):358-363. doi:10.1002/(sici)1097-0142(20000115)88:2<358::aid-cncr16>3.0.co;2-o

18. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future. *J Gastrointest Oncol*. 2016;7(1):143-157. doi:10.3978/j.issn.2078-6891.2015.112

19. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol*. 2016;17(12):1709-1719. doi:10.1016/S1470-2045(16)30500-9

20. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer With Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis. *J Clin Oncol*. 2019;37(23):2028-2040. doi:10.1200/JCO.18.01688

21. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med*. 2018;378(3):230-240. doi:10.1056/NEJMoa1708618

22. Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):256-266. doi:10.1016/S1470-2045(20)30599-4

23. Solaß W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. *Surg Endosc*. 2012;26(7):1849-1855. doi:10.1007/s00464-012-2148-0

24. Suivi à long terme du patient oncologique : enjeux et défis. Revue Medicale Suisse. Accessed September 26, 2022. https://www.revmed.ch/revue-medicale-suisse/2017/revue-medicale-suisse-563/suivi-a-long-terme-du-patient-oncologique-enjeux-et-defis

25. La recherche clinique · Inserm, La science pour la santé. Inserm. Accessed October 11, 2022. https://www.inserm.fr/nos-recherches/recherche-clinique/la-recherche-clinique/

26. Article L1121-1 - Code de la santé publique - Légifrance. Accessed October 11, 2022. https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000032722870/2017-06-14/

27. Møiniche S, Bülow S, Hesselfeldt P, Hestbaek A, Kehlet H. Convalescence and hospital stay after colonic surgery with balanced analgesia, early oral feeding, and enforced mobilisation. *Eur J Surg*. 1995;161(4):283-288.

28. Kehlet H. Fast-track colorectal surgery. *Lancet*. 2008;371(9615):791-793. doi:10.1016/S0140-6736(08)60357-8

29. Réhabilitation améliorée après chirurgie | Livre | 9782294761775. Elsevier Masson SAS. Accessed October 25, 2022. https://www.elsevier-masson.fr/rehabilitation-amelioree-apres-chirurgie-9782294761775.html

30. Alfonsi P, Slim K, Chauvin M, et al. [Guidelines for enhanced recovery after elective colorectal surgery]. *Ann Fr Anesth Reanim*. 2014;33(5):370-384. doi:10.1016/j.annfar.2014.03.007

31. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clin Nutr*. 2010;29(4):434-440. doi:10.1016/j.clnu.2010.01.004

32. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg*. 2009;144(10):961-969. doi:10.1001/archsurg.2009.170

33. Noba L, Rodgers S, Chandler C, Balfour A, Hariharan D, Yip VS. Enhanced Recovery After Surgery (ERAS) Reduces Hospital Costs and Improve Clinical Outcomes in Liver Surgery: a Systematic Review and Meta-Analysis. *J Gastrointest Surg*. 2020;24(4):918-932. doi:10.1007/s11605-019-04499-0

34. Masson E. Aspects économiques de la réhabilitation améliorée après chirurgie. EM-Consulte. Accessed September 22, 2022. https://www.em-consulte.com/article/984929/aspects-economiques-de-la-rehabilitation-amelioree

35. Davigo A, Passot G, Vassal O, et al. PIPAC versus HIPEC: cisplatin spatial distribution and diffusion in a swine model. *Int J Hyperthermia*. 2020;37(1):144-150. doi:10.1080/02656736.2019.1704891

36. Khomyakov V, Ryabov A, Ivanov A, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and Doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). *Pleura Peritoneum*. 2016;1(3):159-166. doi:10.1515/pp-2016-0017

37. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. *J Gastrointest Surg*. 2016;20(2):367-373. doi:10.1007/s11605-015-2995-9

38. Tempfer CB, Celik I, Solass W, et al. Activity of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent, platinum-resistant ovarian cancer: preliminary clinical experience. *Gynecol Oncol*. 2014;132(2):307-311. doi:10.1016/j.ygyno.2013.11.022

39. Tempfer CB, Winnekendonk G, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. *Gynecol Oncol*. 2015;137(2):223-228. doi:10.1016/j.ygyno.2015.02.009

40. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. *Colorectal Dis*. 2016;18(4):364-371. doi:10.1111/codi.13130

41. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). *Clin Exp Metastasis*. 2017;34(5):309-314. doi:10.1007/s10585-017-9849-7

42. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. *PLoS One*. 2017;12(10):e0186709. doi:10.1371/journal.pone.0186709

43. Falkenstein TA, Götze TO, Ouaissi M, Tempfer CB, Giger-Pabst U, Demtröder C. First Clinical Data of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) as Salvage Therapy for Peritoneal Metastatic Biliary Tract Cancer. *Anticancer Res*. 2018;38(1):373-378. doi:10.21873/anticanres.12232

44. Alyami M, Sgarbura O, Khomyakov V, et al. Standardizing training for Pressurized Intraperitoneal Aerosol Chemotherapy. *Eur J Surg Oncol*. 2020;46(12):2270-2275. doi:10.1016/j.ejso.2020.05.007

45. Alyami M, Bonnot PE, Mercier F, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. *Eur J Surg Oncol*. 2021;47(1):123-127. doi:10.1016/j.ejso.2020.05.021

46. Alyami M, Hübner M, Grass F, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. *Lancet Oncol*. 2019;20(7):e368-e377. doi:10.1016/S1470-2045(19)30318-3

47. Kepenekian V, Péron J, You B, et al. Non-resectable Malignant Peritoneal Mesothelioma Treated with Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Plus Systemic Chemotherapy Could Lead to Secondary Complete Cytoreductive Surgery: A Cohort Study. *Ann Surg Oncol*. 2022;29(3):2104-2113. doi:10.1245/s10434-021-10983-2

48. Solass W, Kerb R, Mürdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. *Ann Surg Oncol*. 2014;21(2):553-559. doi:10.1245/s10434-013-3213-1

49. Javanbakht M, Mashayekhi A, Branagan-Harris M, et al. Cost-effectiveness analysis of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with gastric cancer and peritoneal metastasis. *Eur J Surg Oncol*. 2022;48(1):188-196. doi:10.1016/j.ejso.2021.08.024

50. Pisarska M, Torbicz G, Gajewska N, et al. Compliance with the ERAS Protocol and 3-Year Survival After Laparoscopic Surgery for Non-metastatic Colorectal Cancer. *World J Surg*. 2019;43(10):2552-2560. doi:10.1007/s00268-019-05073-0

51. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. *World J Surg*. 2016;40(7):1741-1747. doi:10.1007/s00268-016-3460-y

52. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. *BMJ*. 1997;315(7115):1059. doi:10.1136/bmj.315.7115.1059

53. Alfonsi P, Slim K, Chauvin M, et al. French guidelines for enhanced recovery after elective colorectal surgery. *J Visc Surg*. 2014;151(1):65-79. doi:10.1016/j.jviscsurg.2013.10.006

54. Oliver Goetze T, Al-Batran SE, Pabst U, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naïve upper gi-adenocarcinomas with peritoneal seeding - a phase II/III trial of the AIO/CAOGI/ACO. *Pleura Peritoneum*. 2018;3(2):20180113. doi:10.1515/pp-2018-0113

55. SPF. Survie des personnes atteintes de cancer en France métropolitaine 1989-2018 - Côlon et rectum. Accessed July 28, 2021. https://www.santepubliquefrance.fr/import/survie-des-personnes-atteintes-de-cancer-en-france-metropolitaine-1989-2018-colon-et-rectum

56. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, et al. Association Between Use of Enhanced Recovery After Surgery Protocol and Postoperative Complications in Colorectal Surgery: The Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol (POWER) Study. *JAMA Surg*. 2019;154(8):725-736. doi:10.1001/jamasurg.2019.0995

57. Liu VX, Rosas E, Hwang J, et al. Enhanced Recovery After Surgery Program Implementation in 2 Surgical Populations in an Integrated Health Care Delivery System. *JAMA Surg*. 2017;152(7):e171032. doi:10.1001/jamasurg.2017.1032

58. Ahmed Ali U, Dunne T, Gurland B, Vogel JD, Kiran RP. Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation? *Am J Surg*. 2014;208(4):663-669. doi:10.1016/j.amjsurg.2013.06.004

59. Judith F. Études en vie réelle pour l'évaluation des médicaments et dispositifs médicaux. Published online 2021:51.

60. Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. *Lancet*. 2000;356(9234):968-974.

61. Joris J, Hans G, Coimbra C, Decker E, Kaba A. Elderly patients over 70 years benefit from enhanced recovery programme after colorectal surgery as much as younger patients. *J Visc Surg*. 2020;157(1):23-31. doi:10.1016/j.jviscsurg.2019.07.011

62. Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. *Colorectal Dis*. 2014;16(12):947-956. doi:10.1111/codi.12718

63. Hendry PO, Hausel J, Nygren J, et al. Determinants of outcome after colorectal resection within an enhanced recovery programme. *Br J Surg*. 2009;96(2):197-205. doi:10.1002/bjs.6445

64. Rumstadt B, Guenther N, Wendling P, et al. Multimodal perioperative rehabilitation for colonic surgery in the elderly. *World J Surg*. 2009;33(8):1757-1763. doi:10.1007/s00268-009-0018-2

65. Feroci F, Lenzi E, Baraghini M, et al. Fast-track surgery in real life: how patient factors influence outcomes and compliance with an enhanced recovery clinical pathway after colorectal surgery. *Surg Laparosc Endosc Percutan Tech*. 2013;23(3):259-265. doi:10.1097/SLE.0b013e31828ba16f

66. Baek SJ, Kim SH, Kim SY, Shin JW, Kwak JM, Kim J. The safety of a "fast-track" program after laparoscopic colorectal surgery is comparable in older patients as in younger patients. *Surg Endosc*. 2013;27(4):1225-1232. doi:10.1007/s00464-012-2579-7

67. Lindberg M, Franklin O, Svensson J, Franklin KA. Postoperative pain after colorectal surgery. *Int J Colorectal Dis*. 2020;35(7):1265-1272. doi:10.1007/s00384-020-03580-4

68. Chung F, Chan VW, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. *J Clin Anesth*. 1995;7(6):500-506. doi:10.1016/0952-8180(95)00130-a

69. Ellebæk SB, Graversen M, Detlefsen S, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)-directed treatment of peritoneal metastasis in end-stage colo-

rectal cancer patients. *Pleura Peritoneum*. 2020;5(2):20200109. doi:10.1515/pp-2020-0109

70. Thomassen I, van Gestel YR, van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J Cancer*. 2014;134(3):622-628. doi:10.1002/ijc.28373

71. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg*. 2002;89(12):1545-1550. doi:10.1046/j.1365-2168.2002.02274.x

72. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol*. 2009;27(5):681-685. doi:10.1200/JCO.2008.19.7160

73. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann Oncol*. 2012;23(10):2605-2612. doi:10.1093/annonc/mds203

74. La_lecture_critique_des_essais_cliniques.pdf. Accessed October 13, 2022. https://sofia.medicalistes.fr/spip/IMG/pdf/La_lecture_critique_des_essais_cliniques.pdf

75. Alyami M, Bonnot PE, Mercier F, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for unresectable peritoneal metastasis from gastric cancer. *Eur J Surg Oncol*. 2021;47(1):123-127. doi:10.1016/j.ejso.2020.05.021

76. overview.pdf. https://www.nice.org.uk/guidance/ipg681/documents/overview. Accessed March 21, 2022.

VII. ANNEXES

ANNEXE 1 : Classement des recommandations RAC en fonction de la période opératoire et de leur impact d'après Alfonse et al, 2014[30]

ANNEXE. CLASSEMENT DES RECOMMANDATIONS EN FONCTION DE LA PÉRIODE OPÉRATOIRE ET DE LEUR IMPACT.

Période préopératoire.

Paramètres	Recommandations principales	Recommandations secondaires	Absence de recommandation
Information et conseils au patient	**Oui**		
Préparation colique	**Non** si chirurgie colique		Chirurgie rectale
Prémédication anxiolytique			Absence de données
Jeun préopératoire	**Solides** : 6 heures **Liquides clairs et/ou sucrés** : 2 heures		
Apport en carbohydrates la veille et le matin de l'intervention	**Oui, si** patients ASA I ou 2 **Non, si** patients présentant un diabète ou des troubles de la vidange gastrique		
Immunonutrition	**Oui**, en préopératoire d'une **chirurgie carcinologique** **Non**, en préopératoire d'une **chirurgie non carcinologique** **Non, en postopératoire**		

Période peropératoire.

Paramètres	Recommandations principales	Recommandations secondaires	Absence de recommandation
Apports liquidiens peropératoires	**Oui** : optimisation de la volémie **Non** : un apport excessif de solutés		
Prévention du stress opératoire	**Oui** : dose unique de corticostéroïdes en préopératoire immédiat		
Prévention des infections du site opératoire	**Oui par** La prévention de l'hypothermie peropératoire L'administration d'une antibioprophylaxie		
Prévention des NVPO	**Oui**, systématique		
Voies d'abord chirurgical	**Par laparoscopie**		**Si laparotomie** : aucune recommandation ne peut être faite sur le type d'incision

Période postopératoire.

Paramètres	Recommandations principales	Recommandations secondaires	Absence de recommandation
Sondes nasogastriques	**Non**, à enlever systématiquement en fin d'intervention		
Analgésie postopératoire : Principes généraux	**Analgésie multimodale** privilégiant les agents antalgiques non morphiniques et/ou une technique d'analgésie locorégionale	Prescription d'anti-inflammatoires non stéroïdiens	
Analgésie postopératoire : laparotomie	**Oui** : analgésie péridurale thoracique	1) Irrigation pariétale Ou 2) Lidocaïne intraveineuse Ou 3) Bloc dans le plan du muscle transverse de l'abdomen	
Analgésie postopératoire : laparoscopie	**Oui** : administration intraveineuse continue de lidocaïne **Non** : analgésie péridurale thoracique	1) Irrigation pariétale Ou 2) Le bloc dans le plan du muscle transverse de l'abdomen	
Thromboprophylaxie	**Oui**, par une héparine de bas poids moléculaire à dose prophylactique élevée		
Mise en place d'un drainage chirurgical	**Oui**, si chirurgie avec une anastomose sous-péritonéale **Non**, si chirurgie colique		
Mobilisation précoce	**Oui**, avant h24		
Alimentation orale	**Oui**, à débuter avant h24		
Sondage vésical	**Oui**, si < 24 h après une **chirurgie colique**	Chirurgie du bas rectum : cathéter sus-pubien chez l'homme	
Prévention de l'iléus postopératoire	**Oui** : mastication de gommes (chewing-gum) **Non** : administration de naloxone		

ANNEXE 2 : Check-list de Sécurité Opératoire PIPAC

Check-list de Sécurité Opératoire PIPAC

Faire la vérification de la procédure en binôme (chirurgien et IBODE)

Date :

Identité du patient :

Avant de commencer :

- ☐ **Identité du patient OK ?**
- ☐ Vérification de la procédure chirurgicale prévue OK ?
- ☐ Tout le matériel nécessaire à l'intervention est en salle ?
- ☐ Container à déchets présent ?
- ☐ Draps de protection posés sous l'injecteur et sous la table d'opération ?
- ☐ Arceau mis en place ?
- ☐ Antibioprophylaxie réalisée ?

Préparation de la procédure :

- ☐ Agents chimio thérapeutiques présents en salle d'intervention ou en cours de préparation ? Contrôle de l'étiquetage comprenant le nom du patient, la dose et le contenu.
- ☐ Index de carcinose péritonéale (PCI) et volume de l'ascite documentés ?
- ☐ Biopsies diagnostiques prélevées ?
- ☐ Enregistreur vidéo activé ou photos prises ?
- ☐ **Pneumopéritoine étanche** à 12mmHg CO2 (débit maximum à 0.2L/min)
- ☐ Placement du trocart Blunt tip de 12mm (caméra) : bouchon de perfusion sur le port du ballonnet installé ?
- ☐ Valve fermée ? Tubulure d'aspiration Buffalo installée ?
- ☐ Joint d'étanchéité installé sur le port du trocart ? Caméra insérée dans le trocart et fixée sur l'arceau ?
- ☐ Placement du trocart de 11mm (buse) : bouchon de perfusion sur le port du ballonnet installé ?
- ☐ Adaptation de la tubulure du CO2 au trocart de 11mm (**port d'insufflation ouvert**) ?
- ☐ Housse de caméra fixée sur la buse ?
- ☐ Joint d'étanchéité installé sur le port du trocart ? Buse insérée dans le trocart de 11mm ? Fluctuation libre, pas de contact avec les anses intestinales ?
- ☐ La tubulure connectée est-elle une tubulure de haute pression ? La tubulure est dûment vissée à la buse ?
- ☐ Tubulure d'aspiration Buffalo fixée au champ opératoire ?
- ☐ Housse de protection patient mise en place ?
- ☐ Les tubulures d'aspiration Buffalo sont branchées ? L'aspirateur **Buffalo est allumé** et réglé à 90% ?
- ☐ Instruments, fils et pansements préparés pour la fermeture dans un champ vert ?

Application de la chimiothérapie :

- ☐ **Les membres du personnel sont protégés** : lunette de protection, gants, masque FFP2 et casaques renforcées ?
- ☐ **Vérification des agents chimio thérapeutiques** par rapport à la prescription médicale : nom du patient, dose, contenu, intégrité de la seringue (piston en place ?)
- ☐ Placer les seringues contenant la chimiothérapie dans l'injecteur haute pression ?
- ☐ Connexion de la tubulure à haute pression à la seringue ? Si 2 seringues, un raccord est utilisé ?
- ☐ Mise en place et fixation d'une protection (housse ou champ) à la seringue ?
- ☐ Purger les seringues en circuit fermé
- ☐ Configurer l'injecteur : volume de la seringue, pression max 20 bars ; flux 30ml/min ?
- ☐ Seringues visibles pendant la pulvérisation ?
- ☐ Vérifier les écrans pour monitoring à distance : injecteur, écran vidéo coelio ?
- ☐ **Tous les membres du personnel quittent la salle d'opération**
- ☐ Injection télécommandée (à distance) de la première substance de chimiothérapie
- ☐ Pas de résidus de produit de chimiothérapie dans les seringues et en arrière du piston ?
- ☐ Attendre **30 minutes** après la fin de pulvérisation

Désinstallation :

- ☐ Les chirurgiens et IBO entrent en salle d'opération (masque FFP2, casaques, lunettes, sur-chaussures)
- ☐ **Stopper l'insufflateur CO2**
- ☐ Diriger la caméra en latéral pour éviter l'aspiration du grêle dans le trocart
- ☐ Ouvrir la valve du trocart de caméra et procéder à l'exsufflation de l'aérosol toxique en circuit fermé
- ☐ Fermer le port pour éviter l'aspiration du grêle dans le trocart
- ☐ Placer tout le matériel jetable dans les containers jaunes. **Attention au joint d'étanchéité !**
- ☐ Retirer la seringue de l'injecteur la tête vers le bas

Fin de la procédure :

- ☐ **Tout le personnel entre dans la salle d'opération**
- ☐ Fermer les orifices de trocart

Nom/signature de l'IBODE : **Nom/signature du chirurgien :**

ANNEXE 3 : Valorisation Scientifique de la Thèse

Articles publiés dans le cadre de la thèse :

Tidadini F, Trilling B, Quesada JL, Foote A, Sage PY, Bonne A, Arvieux C, Faucheron JL. Association between Enhanced Recovery After Surgery (ERAS) protocol, risk factors and 3-year survival after colorectal surgery for cancer in the elderly. Aging Clin Exp Res. 2022 Oct 28. doi: 10.1007/s40520-022-02270-1. Epub ahead of print. PMID: 36306111.

Tidadini F, Ezanno AC, Trilling B, Aime A, Abba J, Quesada JL, Foote A, Chevallier T, Glehen O, Faucheron JL, Chkair S, Arvieux C. Hospitalization cost of Pressurized Intraperitoneal Aerosol chemotherapy (PIPAC). Eur J Surg Oncol. 2022 Aug 7: S0748-7983 (22) 00585-6. doi : 10.1016/j.ejso.2022.07.024. Epub ahead of print. PMID : 36 008 216.

Tidadini F, Abba J, Quesada JL, Trilling B, Bonne A, Foote A, Faucheron JL, Arvieux C. Oncological Outcomes After Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in the Treatment of Peritoneal Carcinomatosis. J Gastrointest Cancer. 2022 Jul 1. doi: 10.1007/s12029-022-00843-x. Epub ahead of print. PMID : 35 778 645.

Tidadini F, Abba J, Quesada JL, Villeneuve L, Foote A, Baudrant M, Bonne A, Glehen O, Trilling B, Faucheron JL, Arvieux C. Assessment of postoperative pain after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the treatment of peritoneal metastasis. Int J Colorectal Dis. 2022 May 31. doi: 10.1007/s00384-022-04182-y. Epub ahead of print. PMID : 35 639 123.

Tidadini F, Bonne A, Trilling B, Quesada JL, Sage PY, Foote A, Arvieux C, Faucheron JL. Effect of implementation of enhanced recovery after surgery (ERAS) protocol and risk factors on 3-year survival after colorectal surgery for cancer-a retrospective cohort of 1001 patients. Int J Colorectal Dis. 2022 Apr 26. doi: 10.1007/s00384-022-04155-1. Epub ahead of print. PMID : 35 471 611.

Tidadini F, Abba J, Quesada JL, Baudrant M, Bonne A, Foote A, Faucheron JL, Glehen O, Villeneuve L, Arvieux C. Effect of Pressurized Intraperitoneal Aerosol Chemotherapy on the Survival Rate of Patients with Peritoneal Carcinomatosis of Gastric Origin. J Gastrointest Cancer. 2021 Oct 22. doi: 10.1007/s12029-021-00698-8. Epub ahead of print. PMID : 34 677 795.

Communications Orales :

F. Tidadini, C. Arvieux. Évaluation médico économique de la chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC) dans le traitement de la carcinose d'origine colorectale. **BIG-RENAPE, Association Nationale pour les maladies péritonéales primitives et métastatiques.** Lille, le 10 Juin 2021.

Fatah Tidadini ; Julio Abba ; Jean-Louis Quesada ; Magalie Baudrant ; Aline Bonne ; Alison Foote ; Jean-Luc Faucheron ; Olivier Glehen; Laurent Villeneuve; Catherine Arvieux. Effect of pressurized intraperitoneal aerosol chemotherapy on the survival rate of patients with peritoneal carcinomatosis of gastric origin. **26e Journée Scientifique de L'Ecole Doctorale Interdisciplinaire Sciences Santé (EDISS)**. Lyon, le 18 Novembre 2021.

Fatah Tidadini ; Julio Abba ; Jean-Louis Quesada ; Laurent Villeneuve ; Alison Foote ; Magalie Baudrant ; Aline Bonne ; Olivier Glehen ; Bertrand Trilling ; Jean-Luc Faucheron ; Catherine Arvieux. Évaluation de la douleur post-opératoire après chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC) dans le traitement de la carcinose péritonéale. **12ème Journée du réseau national des tumeurs rares du péritoine**. Lyon, le 28 Janvier 2022.

Fatah Tidadini ; Anne-Cecile Ezanno ; Bertrand Trilling, Adeline Aime ; Julio Abba ; Jean-Louis Quesada ; Alison Foote ; Thierry Chevallier, Olivier Glehen, Jean-Luc Faucheron ; Sihame Chkair ; Catherine Arvieux. Coût d'un séjour hospitalier pour chimiothérapie intrapéritonéale pulvérisée par aérosols (PIPAC) **14ème Journée Francophone des maladies péritonéales primitives et métastatiques – BIG RENAPE.** Paris, le 17 Juin 2022.

Enseignement/Encadrement :

2022 **:** Cours d'Introduction à la recherche clinique aux internes de chirurgie digestive - Université Grenoble-alpes.

2022 : Encadrement d'un stade de formation des investigateurs aux essais cliniques des médicaments (DIU - FIEC) d'une durée de 6 mois, « Impact du retour à domicile précoce après chirurgie colorectale à l'aide d'un dispositif de monitorage de détérioration clinique SENSIUM® ».

Formations :

2022 : Diplôme Universitaire - Méthodologie de la Recherche Clinique, Université d'Amiens

2021 : Manager une équipe-projet, Université de Lyon

2020 : Ethique de la recherche, Université de Lyon - MOOC

2020 : Intégrité scientifique dans les métiers de la recherche, Université de Lyon - MOOC

2020 : Soins palliatifs, Cergy Paris Université - MOOC

2020 : Réhabilitation Améliorée après Chirurgie, Aix-Marseille Université - MOOC