European Journal of Surgical Oncology 45 (2019) 2392–2397

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Early recurrence in peritoneal metastasis of appendiceal neoplasm: Survival and prognostic factors

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ARTICLE INFO

Article history:
Received 8 March 2019
Received in revised form
7 June 2019
Accepted 11 June 2019
Available online 22 June 2019

Keywords:
Appendiceal neoplasm
Cytoreductive surgery
Intraperitoneal chemotherapy
Early recurrence
Peritoneal metastasis
Prognostic factors

ABSTRACT

Introduction: Early recurrence (ER) is defined as development of loco-regional peritoneal disease within 12-month of the initial CRS/PIC. Our aims were to identify overall survival (OS), recurrence-free survival (RFS) and independent prognostic factors associated with ER in PM of appendiceal neoplasm.
Materials and methods: A prospectively-maintained database for patients with appendiceal neoplasm undergoing cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC) from year 1996–2018 was retrospectively analysed.
Results: 208 female and 185 male patients were identified. With a median follow-up of 40-month, 40.2% of the patients developed ER. The median OS for ER was 24 months compared to late (LR) at 64 months. Median OS was not reached in non-recurrence (NR). 5-year survival for ER was less favourable compared to LR and NR (19.3%vs54.6%vs94%). No patients in ER group survived beyond 10-year. Independent negative predictors associated with ER on multivariate analysis were male patient ($p = 0.013$), blood transfusion of >8 units ($p = 0.013$), elevated preoperative CEA levels (>5 ng/ml; $p = 0.002$) and hard intraoperative tumour consistency ($p < 0.001$). Protective factor was a combination of CC1, hard tumour consistency and use of EPIC ($p = 0.039$). Independent prognostic factors that predicted recurrence of appendiceal PM were PCI >20 ($p = 0.049$), non-use of EPIC ($p = 0.012$), hard tumour consistency ($p = 0.004$) and use of previous chemotherapy ($p = 0.023$).
Conclusion: ER following CRS and PIC of appendiceal PM is associated with reduced survival outcomes. Our data alludes to the importance of optimising the risk factors in order to delay loco-regional recurrence and improve long-term survival of these patients.

Introduction

Primary appendiceal neoplasm is not common and represents less than 2% of appendicectomy specimens [1]. Appendiceal tumour has the potential to disseminate into the peritoneal cavity causing peritoneal metastasis (PM) in approximately 20% of patients [2]. Pseudomyxoma peritoneii (PMP) is a malignant condition that is characterised by intraperitoneal accumulation of mucus due commonly to perforated appendiceal neoplasia [3].

The outdated approach to appendiceal PM with repeated interval debulking procedures was a palliative resection of bulky tumour mass, aiming to relieve symptoms of abdominal distension and bowel obstruction. The debulking surgery becomes progressively more complicated, difficult and dangerous with repeated operations [4]. There is also a risk of residual disease dedifferentiating over time to become an invasive adenocarcinoma [5]. Described by Sugarbaker [6] in 1995, cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC) is currently regarded as the standard treatment for appendiceal PM in appropriate patients. The use of intraperitoneal chemotherapy serves to eradicate microscopic neoplastic deposits that are otherwise not resected with CRS. In a large retrospective multi-institutional study of 2298 patients who underwent CRS/PIC for PMP, the median survival rate was 196 months with 10- and 15-year survival rates of

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https://doi.org/10.1016/j.ejso.2019.06.015
0748-7983/

63% and 59%, respectively [7]. Another French multicentre study attained a 5-year survival rate of 73% in 301 patients with diffuse PMP treated with CRS/PIC [8]. .

Recurrence of disease remains a significant problem. Early recurrence (ER) is defined as development of loco-regional peritoneal disease within 12 months of the initial CRS/PIC. This subgroup of patients has a poorer survival outcome than those with recurrence later than 12 months (median overall survival of 38 vs 97 months) [9]. Knowledge regarding ER of appendiceal PM is scarce in the current literature. Effort to define the clinicopathological factors correlated with ER is paramount to facilitate optimisation of patient selection, postoperative outcomes and follow-up prior to undertaking the major procedure. Our primary aim of this study was to identify independent prognostic factors of ER in appendiceal PM. Long-term survival outcomes including overall survival (OS) and recurrence-free survival (RFS) of these patients will also be reported.

Materials and Methods

Patients and selection

From a prospectively maintained database between January 1996 and March 2018, patients with appendiceal neoplasm undergoing CRS with or without PIC at our centre were included in this study. The intraperitoneal chemotherapy regime was guided by the histological subtypes, namely low-grade appendiceal mucinous neoplasm (LAMN) and high-grade appendiceal mucinous neoplasm (HAMN). All patients were thoroughly evaluated for suitability to undergo CRS with or without PIC during weekly multidisciplinary team meeting including surgical and medical oncologists, radiologists, anaesthetists, intensivists, ethicists and other allied health members. They were carefully selected based on a good WHO performance status, absence of significant cardiorespiratory or renal diseases and a histological diagnosis of PM.

Preoperative management

Potential surgical candidates underwent preoperative investigations which included physical examinations, blood tests, computed tomography (CT) scans of the chest, abdomen and pelvis. Additionally, patients with high-grade appendiceal tumours or raised tumour markers underwent either CT portography or MRI primovist and PET scan.

Procedure

Cytoreductive surgery

The extent of peritoneal disease was measured during the laparotomy using the Peritoneal Cancer Index (PCI) [6]. CRS was performed according to the Sugarbaker technique by aiming to remove all macroscopic peritoneal disease [6]. All sites and volumes of residual disease following CRS were recorded prospectively using the completeness of cytoreductive score [10](CC).

Perioperative intraperitoneal chemotherapy

HIPEC was performed in the context of complete cytoreduction (CC0 and CC1). The chemoperfusate was delivered at a temperature of approximately 42 °C using oxaliplatin (350 mg/m2) at a duration of 30 min for HAMN. In contrast, mitomycin C (MMC; 12.5 mg/m2) was used for 90 min in LAMN.

EPIC was used in LAMN or HAMN of soft tumour consistency with 5FU (650 mg/m2) for days 2–6 postoperatively either in the intensive care unit or high dependency unit setting. EPIC was applied to other cancers under certain circumstances, for example, when there is a lack of availability of HIPEC (emergency cases) and contraindication to oxaliplatin or MMC.

Postoperative management

Perioperative complications were classified using the Clavien-Dindo Classification [11] of surgical complications (Grade I: no intervention; Grade II: medical management; Grade III: invasive intervention such as radiological procedures; Grade IV: life-threatening complications warranting urgent return to theatre or ICU admission).

After discharge, follow up was conducted by medical and surgical oncologists to review progress, tumour markers and CT scans (chest, abdomen and pelvis), when appropriate. These patients were scheduled for 3-monthly intervals for first year and then 6-monthly intervals thereafter.

Data

Clinical data for selected patients were extracted from the database. Only patients who underwent index CRS/PIC were included. Exclusion criteria were one of the following: 1) patients who died within a 12-month period from other causes following the initial procedure, 2) those who had isolated or concurrent extra-intestinal relapse, 3) cytoreduction score of >1, 4) those who did not receive HIPEC. Recurrence was diagnosed based on radiological evidence. Relevant patients were stratified into ER and late or no recurrence (LR/NR) groups. LR is defined as PM recurrence later than 12 months. Survival time was obtained in the unit of months from the initial operation to last time of contact or death whereas recurrence-free survival time was calculated in the unit of months from the initial operation to time of recurrence.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 24 (IBM Corporation, New York, USA). Patient characteristics were described using frequency and descriptive analyses. Survival analyses of ER, LR and NR were estimated using the Kaplan-Meier curves and log-rank test for comparison. Clinicopathological factors of patients with ER versus LR/NR were compared using the X^2 test for categorical variables. Significant factors with ER were further analysed using a binary logistic regression model. Similarly, on log-rank test, clinical factors associated with disease recurrence were selected for multivariable analysis using Cox regression model. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The median follow-up post-cytoreduction length for the cohort was 40 months (range: 0–190). There were 208 (52.9%) females and 185 (47.1%) males who underwent CRS/PIC for appendiceal PM. The mean age was 53.62 (SD = 12.82). The mean PCI was 22 (SD = 12). 232 (59.0%) and 159 (40.5%) patients had cytoreduction scores of 0 and 1, respectively.

EPIC was used in 229 cases (58.3%). Postoperatively, patients received care in ICU for a mean of 4 days (SD = 8) and in HDU for a mean of 4 days (SD = 4). The mean length of hospital stay was 28 days (SD = 20).

Survival

Of the 164 patients who developed loco-regional disease

recurrence, 66 of them (40.2%) had ER. Fig. 1 outlines the OS and RFS based on the recurrence status. The overall median survivals for ER and LR were 24 months and 64 months, respectively. It was not reached for NR. 5-year survival for ER was the lowest at 19.3%. No patients survived beyond 10 years. Patients with LR and NR performed more favourably at 5- and 10-year (54.6% vs 94%; 48.5% vs 65.7%) ($p < 0.001$). Meanwhile, patients with ER demonstrated a shorter median RFS at 7 months compared to LR at 27 months (see Table 1).

Prognostic factors for early recurrence

Table 2 highlights the results of both univariate and multivariate analyses. Using the log-rank test, relevant prognostic factors associated with ER were gender ($p = 0.032$), PCI score (0.003), CC-score ($p = 0.001$), use of EPIC($p = 0.041$), elevated preoperative tumour markers including CEA ($p < 0.001$), CA125 ($p = 0.001$), CA19.9 ($p < 0.001$) and a combination of all three (<0.001), histological subtype ($p = 0.002$), previous chemotherapy ($p < 0.001$), synchronous status ($p = 0.006$), amount of blood transfusion ($p < 0.001$), amount of FFP transfusion ($p < 0.001$) and severity of morbidity grade ($p = 0.001$). On multivariate analysis with Cox-regression model of these variables, male gender (OR 2.621, 95% CI = 1.221–5.629, $p = 0.013$), preoperative CEA (>5 ng/ml) (OR 6.508,95%CI = 1.994–21.239,$p = 0.002$), blood transfusion (>8 units) (OR 3.536, 95%CI = 1.300–9.622, $p = 0.013$) and hard tumour consistency (OR 12.410, 95%CI = 3.573–43.102, $p < 0.001$) were predictive of ER in appendiceal PM. Protective factor was a combination of CC1, hard tumour consistency and use of EPIC (OR 0.084, 95%CI = 0.008–0.880, $p = 0.039$).

Prognostic factors for disease recurrence

Clinicopathological factors associated with disease recurrence on univariate analysis were PCI score ($p < 0.001$), cc-score ($p < 0.001$), use of EPIC ($p = 0.001$), elevated preoperative CEA ($p < 0.001$), elevated preoperative CA19.9 ($p < 0.001$), elevated preoperative CA125, three elevated tumour markers (CEA, CA19.9, CA125) ($p < 0.001$), histological subtype ($p < 0.001$), presence of signet ring cells ($p < 0.001$), tumour consistency ($p < 0.001$), previous chemotherapy status ($p < 0.001$), synchronous tumour status ($p < 0.001$), amount of blood transfusion ($p < 0.001$), amount of FFP transfusion ($p < 0.001$) and morbidity grade ($p < 0.001$). When analysed on Cox-regression model, independent prognostic factors that predicted recurrence of appendiceal PM were PCI >20 (HR = 2.274, 95%CI 1.002–5.158, $p = 0.049$), non-use of EPIC (HR = 1.673, 95%CI 1.118 = 2.503, $p = 0.012$), hard tumour consistency (HR = 2.146, 95%CI 1.279–3.601, $p = 0.004$) and use of previous chemotherapy (HR = 1.695, 95%CI 1.077–2.667, $p = 0.023$).

Discussion

The advent of CRS and PIC has significantly improved the survival outcomes of appendiceal PM [7,8]. Unfortunately, relapse of appendiceal PM still occurs prevalently despite such aggressive intervention with reported disease recurrence rates of 26.4%–44% [12,13]. In this study, we investigated survival outcomes of a subgroup of these patients who had loco-regional disease recurrence within 12 months, or simply referred to as ER, following the operation. Our data shows that 40.2% of our patients had disease recurrence a year following CRS and PIC. Overall, the survival outcomes of ER in appendiceal PM were relatively poor. Patients with ER had a lower median OS at 24 months compared to those with diseases which recurred late or did not recur (64 months and not reached). No patients with ER survived beyond 10 years. Clinical factors associated with disease recurrence were PCI>20, non-use of EPIC, hard tumour consistency and use of prior chemotherapy.

There is a paucity of information on the survival outcomes of ER in appendiceal PM following CRS/PIC. To date, we found only two studies that analysed the survival outcomes of PM of appendiceal origin. In a retrospective review of 113 patients with PMP who underwent CRS and PIC, the incidence of developing ER was reported at 49%. According to Chua et al., the median OS in this subgroup was 38 months, which was significantly lower than those who had LR ($p = 0.002$) [9]. Another recent retrospective study [14] of 144 patients with PM secondary to appendiceal, colorectal and ovarian tumours demonstrated a median OS of 27 months in the ER group in relative to 100 months in the group with late or no recurrence after CRS and PIC. The aforementioned papers concurred with our analysis. This information further consolidated the clinical significance of early loco-regional disease recurrence such that ER makes a huge negative impact on the survival outcomes following the initial cytoreduction of appendiceal PM.

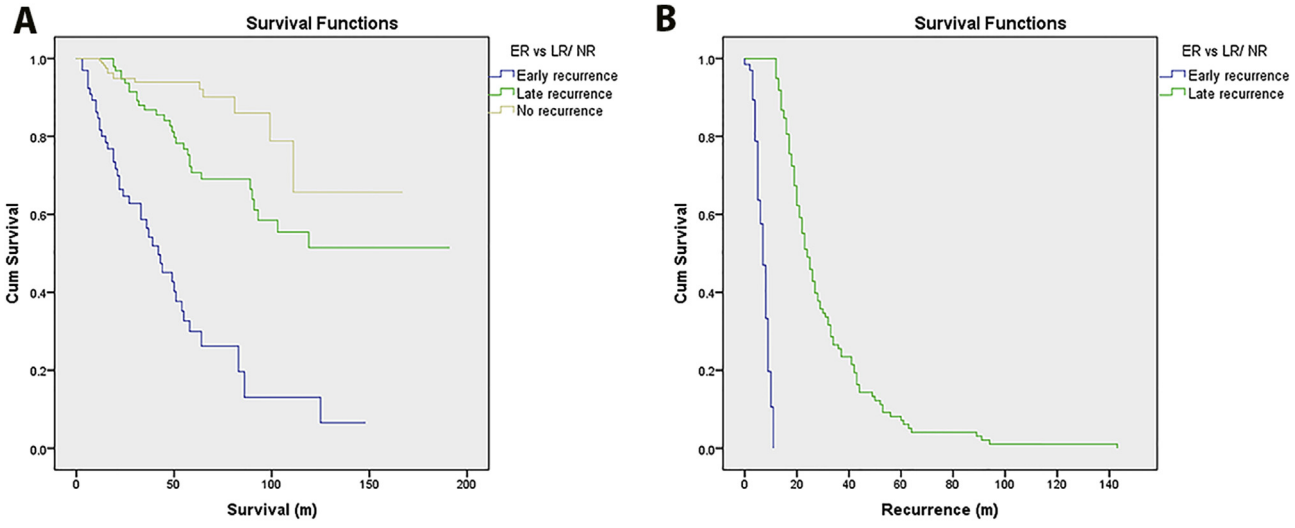

Fig. 1. Kaplan-Meier curves of A) overall survival, B) recurrence-free survival comparing ER, LR and NR.

Table 1
Comparison of clinopathological factors influencing early recurrence and late or no recurrence using X^2.

Clinicopathological factors	Early recurrence	Late or no recurrence	P value
Gender			
Female	27 (13%)	181 (87%)	0.032
Male	39 (21.1%)	146 (78.9%)	
PCI score			
0–10	6 (7.7%)	72 (92.3%)	0.003
11–20	8 (10.1%)	71 (89.9%)	
>20	52 (22.1%)	183 (77.9%)	
cc-score			
0	27 (11.6%)	20.5 (88.4%)	0.001
1	39 (24.5%)	120 (75.5%)	
EPIC			
Yes	35 (21.3%)	129 (78.7%)	0.041
No	31 (13.5%)	198 (86.5%)	
Elevated preoperative CEA			
Yes	51 (26.4%)	142 (73.6%)	<0.001
No	13 (7.1%)	170 (92.9%)	
Elevated preoperative CA19.9			
Yes	39 (30.7%)	88 (69.3%)	<0.001
No	23 (9.5%)	219 (90.5%)	
Elevated preoperative CA125			
Yes	37 (22.7%)	126 (77.3%)	0.001
No	21 (10.3%)	183 (89.7%)	
Three elevated tumour markers (CEA, CA19.9, CA125)			
Yes	26 (31%)	58 (69%)	<0.001
No	34 (11.8%)	253 (88.2%)	
Histological subtype			
HAMN	37 (24.3%)	115 (75.7%)	0.002
LAMN	29 (12.1%)	211 (87.9%)	
Presence of signet ring			
Yes	12 (21.1%)	45 (78.9%)	0.352
No	54 (16.1%)	282 (83.9%)	
Tumour consistency			
Soft	36 (14.4%)	214 (85.6%)	0.021
Hard	20 (28.6%)	50 (71.4%)	
Mixed	5 (15.6%)	27 (84.4%)	
Previous chemotherapy			
Yes	21 (31.3%)	46 (68.7%)	<0.001
No	44 (13.7%)	278 (86.3%)	
Synchronous			
Yes	34 (23.8%)	109 (76.2%)	0.006
No	32 (13%)	215 (87%)	
Blood transfusion			
≤8 units	31 (10.2%)	273 (89.8%)	<0.001
>8 units	35 (39.3%)	54 (60.7%)	
FFP transfusion			
≤10 units	33 (11.2%)	261 (88.8%)	<0.001
>10 units	33 (33.3%)	66 (66.7%)	
Morbidity			
Grade 0-2	23 (10.8%)	189 (89.2%)	0.001
Grade 3-4	43 (23.8%)	138 (76.2%)	

Table 2
Independent predictive factors of early recurrence in appendiceal PM on multivariate analysis.

Factors	OR (95%CI)	P value
Gender (female ref)	2.621 (1.221–5.629)	0.013
PCI		
0-10	Ref	Ref
11-20	1.301 (0.229–7.400)	0.766
>20	1.809 (0.411–7.957)	0.433
cc-score	1.855 (0.766–4.489)	0.171
EPIC	0.831 (0.347–1.989)	0.678
Preoperative CEA	6.508 (1.994–21.239)	0.002
Preoperative CA19.9	1.306 (0.374–4.555)	0.676
Preoperative CA125	0.782 (0.241–2.542)	0.683
Elevated combined tumour markers	1.243 (0.264–5.850)	0.783
Histology	1.165 (0.504–2.693)	0.720
Prior chemotherapy	1.466 (0.598–3.595)	0.403
Synchronous	0.903 (0.400–2.041)	0.807
Morbidity grade	1.433 (0.650–3.160)	0.373
FFP transfusion	1.133 (0.418–3.068)	0.806
Blood transfusion	3.536 (1.300–9.622)	0.013
Tumour character		
Soft	Ref	Ref
Hard	12.410 (3.573–43.102)	<0.001
Intermediate	1.518 (0.301–7.638)	0.613
Interactions of cc-score, EPIC and tumour character		
cc-1, EPIC, hard consistency	0.084 (0.008–0.880)	0.039
cc-1, EPIC, intermediate consistency	0.260 (0.015–4.444)	0.352

The risk factors contributing to recurrence of appendiceal PM within a year have not yet been clarified. In our study, male patients and patients requiring >8 units of blood transfusion - each of which increased the risks of developing ER by approximately three- and four-fold – were two relevant independent negative prognostic factors identified. The association between intraoperative blood transfusion and ER of appendiceal PM in this series is intriguing. Recently, the negative effects of perioperative blood transfusion on the surgical outcomes of various oncological procedures have been extensively studied and documented [15–17]. At our institution, we noted massive blood transfusion (≥5 units) was associated with in a suboptimal perioperative outcomes including in-hospital mortality (relative risk: 7.72, $p = 0.021$) and grade III/IV morbidity (RR: 2.05, $p < 0.001$) [18]. 5-year survival rate was significantly lower in massive blood transfusion group for patients with colorectal PM (5% vs 36%) and PMP (63% vs 98%). Nizri et al. analysed 231 patients with diffuse malignant peritoneal mesothelioma and 273 patients with PMP treated with CRS and PIC. They showed that blood transfusion is an independent prognostic factor for worse OS and RFS. It has a dose-dependent effect such that even low amount of transfusion (1U–2U) compromises survival outcomes following CRS and PIC of peritoneal malignancy [19]. The relationship of early relapse in appendiceal PM and intraoperative blood transfusion could be explained by a phenomenon known as transfusion-related immune modulation (TRIM). The inflammatory and immunosuppressive nature of blood products create an environment that promotes growth of malignant cells in which many biological factors have the potential to blunt the recipients' innate immunity which is imperative for local tumour control [20].

Preoperative and postoperative tumour markers (CEA, CA19.9 and CA125) serve as a measure to aid diagnosis of malignancy, assess response to treatment and detect tumour recurrence. Our data suggested that elevated preoperative CEA (>5 ng/ml) was a predictive factor for ER of appendiceal PM with a significant six-fold increase in risk (OR 6.51, 95%CI 2.0–21.2, $p = 0.002$). The importance of preoperative CEA level in appendiceal peritoneal malignancy was previously described by several institutions [21,22]. In a small series of thirty-five PMP patients following CRS/PIC, Alexander-Sefre et al. reported that elevated CEA increased the likelihood of developing PMP recurrence by 5.6 times. These patients also had significantly shorter disease-free interval ($p = 0.003$). A larger series of 449 PMP patients in Japan concluded that CEA levels was predictive of recurrence of disease after complete cytoreduction (OR 2.2, 95% CI 1.39–3.17, $p < 0.001$). CEA was associated with disease progression and survival [22]. The significance of CA125 and CA125 in the surveillance of appendiceal PM could not be downplayed [23,24]. Among 176 patients undergoing CRS/PIC for appendiceal carcinomatosis, Wagner and colleagues claimed that elevated CA19.9 was independently associated with shorter RFS (OR 2.9,95%CI 1.5–5.3, $p < 0.001$) while elevated CA125 was associated with shorter OS (OR2.6,95%CI 1.3–5.4, $p = 0.01$) [25]. Taflampas et al. concluded that elevated preoperative tumour markers had a significant negative impact on RFS and OS which was more marked with increasing number of different raised tumour markers [26].

PM of appendiceal neoplasm is categorised pathologically as LAMN and HAMN [27]. The former is characterised histologically by adenomatous mucinous epithelium within abundant extracellular mucin. Meanwhile, the latter demonstrates more abundant mucinous epithelium forming glands and cytologic atypia of mucinous carcinoma. There is also an inherent biologic difference between the two with high-grade tumours known to behave more aggressively than its counterpart [28]. The documented 5-year survival rates for high-grade tumours range from 14 to 59% as opposed to 75–83% in low-grade tumours across various literature [2,7,28,29]. Given the nature of HAMN, we were surprised that even though there was a link between HAMN with early recurrence of appendiceal PM within a year (24.3% vs 75.7%, $p = 0.005$), the difference was not large enough to be significant as an independent prognostic factor. Furthermore, no correlation was found between PCI and ER on multivariate analysis although the implication of PCI in the survival outcomes of appendiceal tumours is well-established [7].

Intraoperatively, appendiceal PM can present in three variable textures: soft gelatinous, hard and firm or a combination of soft and hard components (intermediate). Whereby microscopic feature of peritoneal appendiceal neoplasm is a well-known prognostic factor on the survival outcomes of these patients, the influence of macroscopic appearance is not widely recognised. Here, we found that tumour with hard consistency was a negative predictive factor for ER of appendiceal PM (OR 12.4, 95%CI 3.6–43.1, $p < 0.001$) and associated with poor recurrence free survival (HR = 2.146, 95%CI 1.279–3.601). A recent study from our centre [30] highlighted that hard tumours were associated with a shorter OS (HR 4.43, 95%CI 2.19–9, $p < 0.001$) on multivariate analysis. The mechanism by which hard tumours contribute to a worse survival is unclear. However, Huang et al. hypothesised that tumour texture may define the compactness of mucin which acts as a protective barrier that will hinder the efficacy of chemotherapy.

The use of EPIC is less popular in the treatment of PM in recent times due to its association with higher complication rates and prolonged hospital admission [31,32]. In a series of ninety-three patients who underwent CRS, EPIC was reported to offer no survival benefit [33] in addition to HIPEC. Nevertheless, the analysis included only patients with colorectal or high-grade appendiceal carcinomatosis. At our institution, we strongly advocate EPIC for patients with LAMN. Our prior data [34] highlighted a marked improvement in 5-year OS for patients with LAMN who received a combined HIPEC and EPIC therapy than those who received HIPEC alone (93.0% vs. 64.5%; $p < 0.001$) with no significant differences in mortality and morbidity between two groups. Although EPIC is not an independent prognostic factor for ER of appendiceal PM in this study, we demonstrated that non-use of EPIC was associated with appendiceal PM recurrence. We are also strong advocates of EPIC for HAMN of soft tumour consistency, accepting patients with cc-score below 2 (<CC2). The aforementioned study suggested that HAMN with soft tumour consistency behaves biologically as LAMN [30] and use of both EPIC and HIPEC were associated with a significant improvement in OS in these patients ($p = 0.005$). Therefore, we wonder if there is any interaction of EPIC with tumour consistency and CC-scores. Our investigation on multivariate analysis revealed that EPIC was associated with a marked reduced risk of developing ER in appendiceal PM (OR 0.084, 95%CI 0.008–0.880, $p = 0.039$) when applied to patients with hard tumours and CC1 (Table 2). This is perhaps clinically relevant as the administration of EPIC in patients with hard tumours and CC1 may be beneficial from oncological point of view, delaying the recurrence of appendiceal PM.

The administration of chemotherapy prior to the index CRS/PIC was an independent poor prognostic factor for recurrence of appendiceal PM (HR = 1.695, 95%CI 1.077–2.667, $p = 0.023$). This is consistent with the findings of several publications [7,35–37]. Several possible reasons may explain this phenomenon. First, previous use of systemic chemotherapy may signify high grade or aggressive tumour pathology. In our study, patients with HAMN who received preoperative chemotherapy was significantly higher compared to LAMN ($p < 0.001$). Besides, systemic chemotherapy could potentially eradicate chemosensitive cells and aid in the selection of chemoresistant clones which propagates its growth. Lastly, previous chemotherapy was also inclined to be commenced in peripheral hospitals hence delaying access to curative surgery.

Currently, iterative CRS/PIC as a treatment of local disease recurrence can be offered to patients in our centre provided they have good functional status. However, as pointed out by Konstantinidis et al., the time interval between the initial and repeat cytoreductive surgery is important [38]. They reported a significantly lower median OS at 1.3 years when the repeat procedure happens <1 year compared to 3.7 years and 7 years for interval of 1–2 years and >2 years, respectively. An interval >2 years between cytoreductions has been shown to confer a better prognosis independently ($p = 0.0002$). Therefore, addressing the prognostic factors of ER may help delay early recurrence, optimise outcome and improve long-term survival of these patients. In particular, the use of intraoperative blood transfusion should be optimised appropriately. In our centre, routine iron transfusion is administered for anaemic patients preoperatively. A new development lately has implied a possible role of upfront tranexamic acid and cryoprecipitate during peritoneal surgery in reducing the amount of intraoperative blood transfusion [39]. In a matched retrospective study, Sargant and his colleagues demonstrated a reduction in the number of patients requiring massive transfusion under its new transfusion protocol (7% vs 29%). No patients required >8U of red cells compared to 15% on the standard protocol. The finding was encouraging and more research is warranted to validate this in the future.

This study has several limitations. First, selection bias may be introduced inadvertently due to the retrospective nature of this series and the data should be interpreted with caution. Also, there was a paucity of information, including the interval of appendiceal PM diagnosis to initial cytoreduction, which restricted the versatility of our analysis. The lack of uniform classifications of appendiceal PM historically could possibly have led to some inconsistencies in the histological subtyping of surgical specimens.

Conclusion

Early recurrence of appendiceal PM within a year is prevalent following CRS and PIC. This study highlights the poor survival prognosis associated with such occurrence. The independent negative predictors identified for ER are male gender, blood transfusion of >8U, elevated preoperative CEA level of >5 ng/ml and hard intraoperative tumour consistency. Protective factor was a combination of CC1, hard tumour consistency and use of EPIC. Independent prognostic factors that predicted recurrence of appendiceal PM were PCI >20 ($p = 0.049$), non-use of EPIC ($p = 0.012$), hard tumour consistency ($p = 0.004$) and use of previous chemotherapy ($p = 0.023$). Our data alludes to the importance of optimising the risk factors in order to delay loco-regional recurrence and improve long-term survival of these patients.

Conflicts of interest

None to declare.

Sources of support

No funding. No financial relationships.

Ethics approval

Ethical approval was sought for recruitment of patients into database through South Eastern Sydney Local Health District Human Research Ethics Committee.

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