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Impact of Macroscopic Tumour Consistency and EPIC in Low-grade Appendiceal Neoplasms With Pseudomyxoma Peritonei

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Abstract. *Background/Aim: Low-grade appendiceal mucinous neoplasm (LAMN) with pseudomyxoma peritonei (PMP), otherwise known as disseminated peritoneal adenomucinosis (DPAM), is treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with or without early postoperative intraperitoneal chemotherapy (EPIC). These tumours can vary significantly intraoperatively in terms of macroscopic appearance and consistency, and this may have an effect on survival outcomes. This study examines the differences between soft and hard tumours in terms of short-term outcomes and long-term survival and whether this can change with the use of EPIC. Patients and Methods: Patients were classified into having macroscopically soft or hard tumours. A comparison of short-term outcomes (major morbidity, mortality, length of ICU stay and length of hospital stay) and long-term outcomes (overall survival) was performed. Survival sub analysis was performed in the patients who received EPIC. Results: Soft tumours behaved differently, with lower morbidity, mortality, shorter ICU stay and hospitalisation. They also demonstrated greater overall survival (86.7% at 5 years, p<0.001). EPIC improved the overall survival for both soft and hard tumours. Conclusion: Tumour consistency has an impact on the outcomes of patients with DPAM and this can be used for prognostication.*

Low-grade appendiceal mucinous neoplasms (LAMNs) are rare tumours of the appendix which can perforate and cause peritoneal spread of mucinous ascites called pseudomyxoma peritonei (PMP) (1). The most recent Peritoneal Surface Oncology Group International (PSOGI) meeting classified PMP into several distinct entities. One such entity is LAMN with peritoneal spread, otherwise known as disseminated peritoneal adenomucinosis (DPAM). DPAM demonstrates histological features of "pushing invasion" via extrusion of epithelial cells, rather than infiltrative destruction which is seen in high grade PMP or peritoneal mucinous carcinomatosis (PMCA) (2). Thus, DPAM results in widespread mucinous spread and accumulation of mucinous ascites intraperitoneally. It is associated with poor patient survival if not treated surgically with aggressive tumour debulking (3).

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have evolved into the standard of care for DPAM and have demonstrated excellent long-term survival, with a reported 5-year overall survival (OS) ranging from 50% to 86% and 10-year OS of 45% to 68% (1, 4, 5). The delivery of intraperitoneal chemotherapy in HIPEC counteracts the poor penetrance of systemic chemotherapy for targeting peritoneal tumour cells. In addition to this benefit, the use of heat further sensitises the mitochondria of malignant cells and potentiates the efficacy of intraperitoneal chemotherapy through a synergistic effect (6). However, the effect of HIPEC can only be delivered intraoperatively, for a short period of time. Therefore, the addition of early postoperative intra-peritoneal chemotherapy (EPIC) aims to increase peritoneal exposure of chemotherapeutic agents whilst minimising systemic toxicity (7, 8). EPIC is therefore particularly important for DPAM due to its propensity for local peritoneal metastasis and subsequent poor response to systematic chemotherapy (9).

DPAM remains a pathologically diverse disease with broad clinical and histopathological features. There are still several unknown variables that may impact patient survival (10). We propose that macroscopic tumour variation may impact the degree of penetration that intraperitoneal

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chemotherapy has on the tumours, and subsequently influence treatment efficacy. Our previous study examined the tumour consistency of appendiceal adenocarcinomas with peritoneal metastasis and demonstrated a greater OS in patients with soft tumours and patients who had received EPIC (11). The current study postulates that macroscopically soft and hard DPAM behave differently and thus impacts patient outcomes and long-term survival.

Patients and Methods

Patient selection. Patients that underwent CRS and HIPEC for DPAM between January 1996 and March 2022 were identified. Data was collected retrospectively from a prospectively maintained database at the Peritonectomy Unit of St. George Hospital. Operation reports for each patient were examined by two surgeons. Soft tumours were described either as "soft, gelatinous, or furry" and hard tumours were described as "hard, firm, or nodular". Patients were divided into two groups ("soft" and "hard") according to the macroscopic description on their operation report. Figure 1 outlines the patient selection and grouping process.

Pre-operative management. All patients underwent a comprehensive preoperative work up including blood tests, tumour markers, computed tomography (CT) imaging of chest, abdomen, and pelvis and, if required, magnetic resonance imaging (MRI) of the liver and positron emission tomography (PET) scans. Prior to surgery, all patients' conditions were discussed at a multi-disciplinary meeting with surgeons, medical oncologists, radiologists, and allied health staff.

Cytoreductive surgery. All patients underwent CRS in accordance with the principles outlined by Sugarbaker *et al.* (12). The peritoneal cancer index (PCI) score was used to grade the volume of disease and was calculated at the beginning of each operation. A PCI score out of 39 is calculated by dividing the abdomen into 13 regions and assigning a score of 0-3 depending on tumour size (13). Following CRS, the degree of macroscopic resection was graded using the completeness of cytoreduction (CC) score, which ranges from 0 to 3, based on the size of macroscopic tumour disease at the end of the CRS. CC-0 score indicates no residual disease, CC-1 score indicates remaining disease less than 2.5 mm, CC-2 score indicates remaining disease ranging between 2.5 mm and 25mm and CC-3 score indicates remaining disease over 25 mm (13).

Hyperthermic intraperitoneal chemotherapy. After completion of CRS, HIPEC was administered in a standardised manner. The Coliseum technique (open method) was used at our institution. The abdomen was primed with Dianeal PD4 (1.5%) Peritoneal Dialysis Solution and heated to 41.5˚C. Once the target temperature was achieved, the chemotherapeutic agent was administered and stirred every 15 min to provide an even chemotherapeutic distribution. The agents used were either Mitomycin C (12.5 mg/m^2) for 90 min or Oxaliplatin (350 mg/m^2) for 30 min.

Early postoperative intraperitoneal chemotherapy (EPIC). A strict criterion was required for both the initiation and continuation of EPIC. A leak test was performed to ensure there was no leakage around drain sites on day one after the operation. For EPIC to proceed, an absence of leakage, no major organ failure, no evidence of sepsis, normal intraabdominal pressure (under 20 mmHg), adequate urine output (over 0.5 ml/kg/h) and the ability to tolerate the volume of administered intra-abdominal fluid was required. The number of days EPIC was administered varied between 2 and 5.

The delivery of EPIC was through a peritoneal (Argyle™ Tenckhoff, Medtronic, Minneapolis, MN, USA) catheter placed intraoperatively. All the sump drains were clamped and 5-Fluororacil chemotherapy at 650 mg/m^2 with 50 mEq of sodium bicarbonate was administered. After 23 h, the chemotherapy was released through the abdominal drains and the next cycle of intraperitoneal chemotherapy was administered. The entire duration of EPIC was performed in the intensive care unit setting.

Post-operative management. All postoperative complications were recorded based on the Clavien-Dindo Classification (CDC) (14). Major morbidity was defined as CDC grade III or IV. Mortality was classified as any death that occurred during the index admission or within 90 days of the operation. Length of ICU stay was calculated based on the total days spent in the ICU during index admission. Total length of hospital stay was calculated from the date of surgery to the date of discharge from hospital.

Routine follow up was conducted on a three-monthly basis for 5 years comprising of a physical examination, tumour markers and CT imaging. After 5 years patients would continue yearly follow ups with the surgical or medical oncology team.

Statistical analysis. All statistical analyses were performed using IBM SPSS software version 24 (IBM corporation, New York, NY, USA). Descriptive statistics included mean, percentage, standard deviation (SD) and range. Categorical variables were compared using the Pearson Chi-square test or Fisher' exact test, where appropriate. Continuous variables were compared using student *t*-test or one-way analysis of variance (ANOVA). The Cox regression model for proportional hazard ratio was used to measure the probability of survival at a given time with both univariate and multivariate analysis. Survival analyses were represented using Kaplan-Meier curves. Statistical significance was defined at $p<0.05$.

Results

Patient characteristics. A total of 246 patients were identified with DPAM and underwent CRS and HIPEC. 197 of those patients had accurately recorded tumour consistency on their operation report. Overall, there were 153 patients with soft tumours and 44 patients with hard tumours. Table I summarises the patient demographics and a comparison of the two groups.

Of those with soft tumours, 120 (78.4%) received EPIC and 33 (21.6%) did not. Fourteen (31.8%) patients with hard tumours received EPIC whilst 30 (68.2%) did not. Mean age was 54.6 years (SD 14.3) with no difference between the two groups ($p=0.153$). The majority of patients had a PCI of 21 and above (62.7% in soft tumours and 70.5% in hard tumours, $p=0.663$). The percentage of CC-0 and CC-1+ was similar between both groups ($p=0.116$). A proportionally greater number of patients with soft tumours received EPIC compared to those with hard tumours ($p<0.001$). Operative time was longer in hard tumours compared to soft (9.6 hours *vs.* 8.6 hours, $p=0.019$).

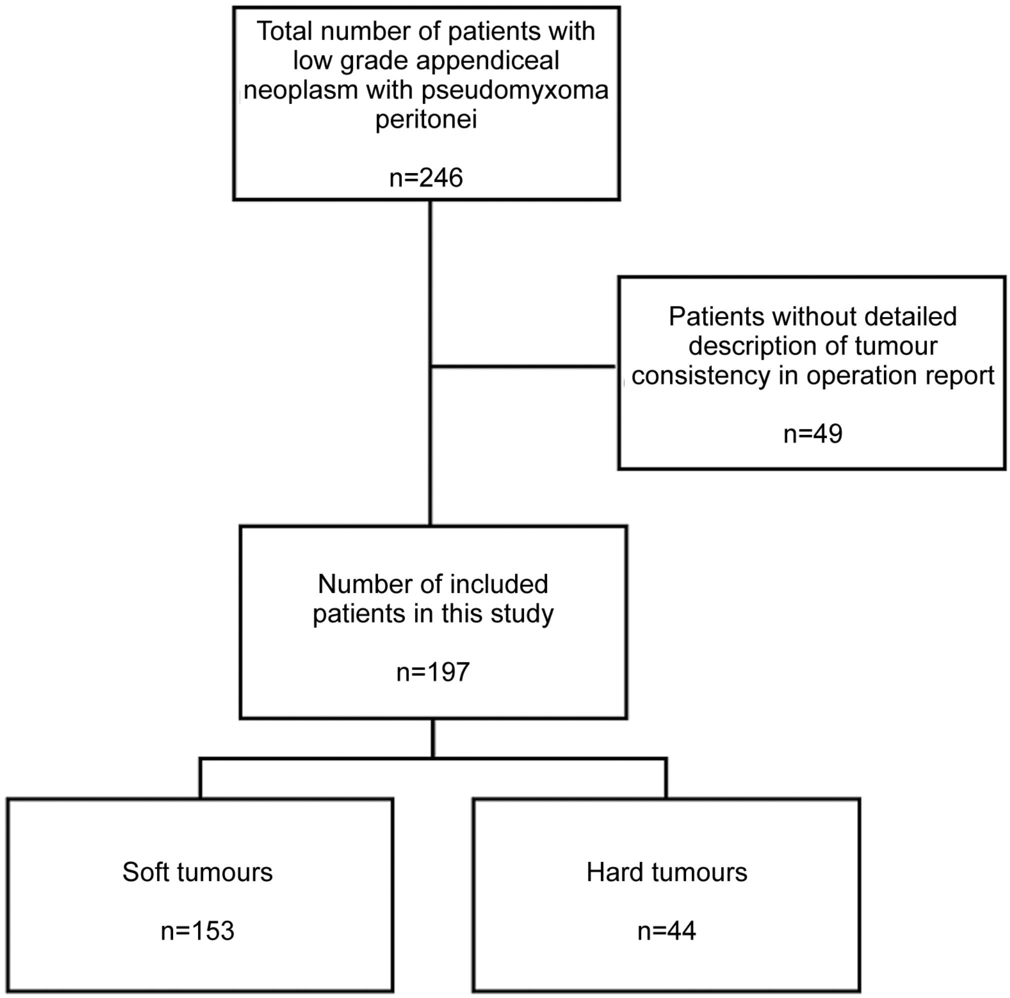

Figure 1. *Flow diagram demonstrating the selected patients for analysis.*

Morbidity and mortality. The overall morbidity (CDC III/IV) of patients with DPAM was 33.0% (n=65) and mortality was 2.5% (n=5). Hard tumours had a higher percentage of Grade III/IV complications (54.5%) compared to soft tumours (25.8%) and this was statistically significant ($p<0.001$). Patients with hard tumours also recorded higher mortality compared to soft tumours (Table II). A total of 5 patient deaths were recorded with 4 occurring in the hard tumour group and 1 in the soft ($p=0.002$). ICU stay was longer in hard tumours (10.4 days *vs*. 3.38 days, $p=0.011$), as was overall length of hospital stay (36.3 days for hard tumours *vs*. 25.19 days for soft tumours, $p=0.002$).

Survival outcomes. The mean OS was 176.4 months with median OS not reached at the time of analysis. OS at 1, 3 and 5 years was 95.4%, 92.4% and 86.7%, respectively. There was a longer mean OS in the soft tumour group of 196 months compared to 114 months for hard tumours ($p<0.001$) (Figure 2A). The median OS was not reached by soft tumours but was 103.6 months for hard tumours. Patients who received EPIC demonstrated improved mean OS compared to those who did not (189.2 months *vs*. 67.8 months, $p<0.001$) (Figure 2B). Again, the median OS was not reached by those who received EPIC and was 91.6 months for those who did not receive EPIC.

A multivariable analysis demonstrated that tumour consistency, EPIC and completeness of cytoreduction were independent factors that impacted OS (Table III). The hazard ratio (HR) for hard tumours over soft tumours was 4.25 [95% confidence interval (CI)=1.87-9.64, $p<0.001$]. Comparing those who received EPIC to those who did not, the HR was 0.342 (95% CI=0.126-0.830, $p=0.019$). Those with a CC score of 1+ had a HR of 2.59 compared to CC-0 (95% CI=1.01-6.62, $p=0.47$).

Table I. *Description of baseline characteristics of all patients and comparison between soft and hard tumours.*

	Soft tumours n=153	Hard tumours n=44	Total n=197	*p*-Value
Mean age in years (SD)	53.8 (14.4)	57.3 (13.7)	54.60 (14.3)	0.153
Sex n (%)				
Male	85 (55.6)	22 (50.0)	107 (54.3)	0.514
Female	68 (44.4)	22 (50.0)	90 (45.7)	
EPIC, n (%)				
Yes	120 (78.4)	14 (31.8)	134 (68.0)	<0.001
No	33 (21.6)	30 (68.2)	63 (32.0)	
PCI score, n (%)				
0-20	57 (37.3)	13 (29.5)	70 (35.5)	0.663
21-39				
94 (62.7)	31 (70.5)	125 (64.5)		
CC score, n (%)				
CC 0	90 (58.8)	20 (45.5)	110 (55.8)	0.116
CC 1+	63 (41.2)	24 (54.5)	87 (44.2)	
Operative hours (Mean, SD)	8.64 (2.2)	9.6 (2.8)	8.98 (2.4)	0.019

EPIC: Early postoperative intraperitoneal chemotherapy; PCI: peritoneal cancer index; CC: completeness of cytoreduction; SD: standard deviation.

Table II. *Comparison of major morbidity, mortality and length of hospital stay in soft and hard tumours.*

Variable	Soft tumours	Hard tumours	*p*-Value
Major morbidity (Grade III or IV) n (%)	41 (26.8)	24 (54.5)	<0.001
Mortality, n (%)	1 (0.654)	4 (9.09)	0.002
ICU stay in days (median)	3.38 (3.04)	10.41 (17.431)	0.011
Hospital length of stay in days (median)	25.19 (16.9)	36.3 (20.85)	0.002

Subgroup analysis. As both tumour consistency and EPIC influenced OS, we performed subgroup analysis stratifying EPIC status with tumour consistency. For all patients who received EPIC, those with soft tumours demonstrated greater OS compared to hard tumours (p<0001) (Figure 3A). In hard tumours alone, those who received EPIC demonstrated improved OS compared to those who did not (p<0.001) (Figure 3B). Patients with soft tumours that received EPIC demonstrated the best long-term survival with a 5-year OS of 94% (Table IV).

Table III. *Cox regression multi-variable analysis of prognostic factors for overall survival.*

Characteristics	Multivariable HR (95% CI)	*p*-Value
Tumour consistency		
Soft[a] *vs*. Hard	4.251 (1.873-9.644)	*p*<0.001
Epic		
Yes[a] *vs*. No	0.342 (0.126-0.830)	*p*=0.019
PCI score		
0-20[a] *vs*. 21-39	2.835 (0.635-12.657)	*p*=0.172
CC Score		
CC 0[a] *vs*. CC 1+	2.588 (1.011-6.623)	*p*=0.047

[a]Reference group. HR: Hazard ratio; CI: confidence interval; PCI: peritoneal cancer index; CC: completeness of cytoreduction.

Discussion

Appendiceal tumours presenting as PMP exhibit a diverse spectrum of clinicopathological behaviour (10). This ranges from relatively slow growing tumours without significant invasive features to highly aggressive tumours with behaviour more akin to colorectal adenocarcinomas (15). Traditionally, predicting tumour behaviour and patient outcomes has relied on histological and morphological characteristics, in addition to molecular tumour mutation analysis (1, 10, 15). Few studies have utilised intraoperative macroscopic appearance and consistency of tumours in order to predict behaviour and prognosis (11, 16).

In this study, we found that soft tumours in DPAM resulted in significantly better OS compared to hard tumours. Furthermore, hard tumours were associated with a higher

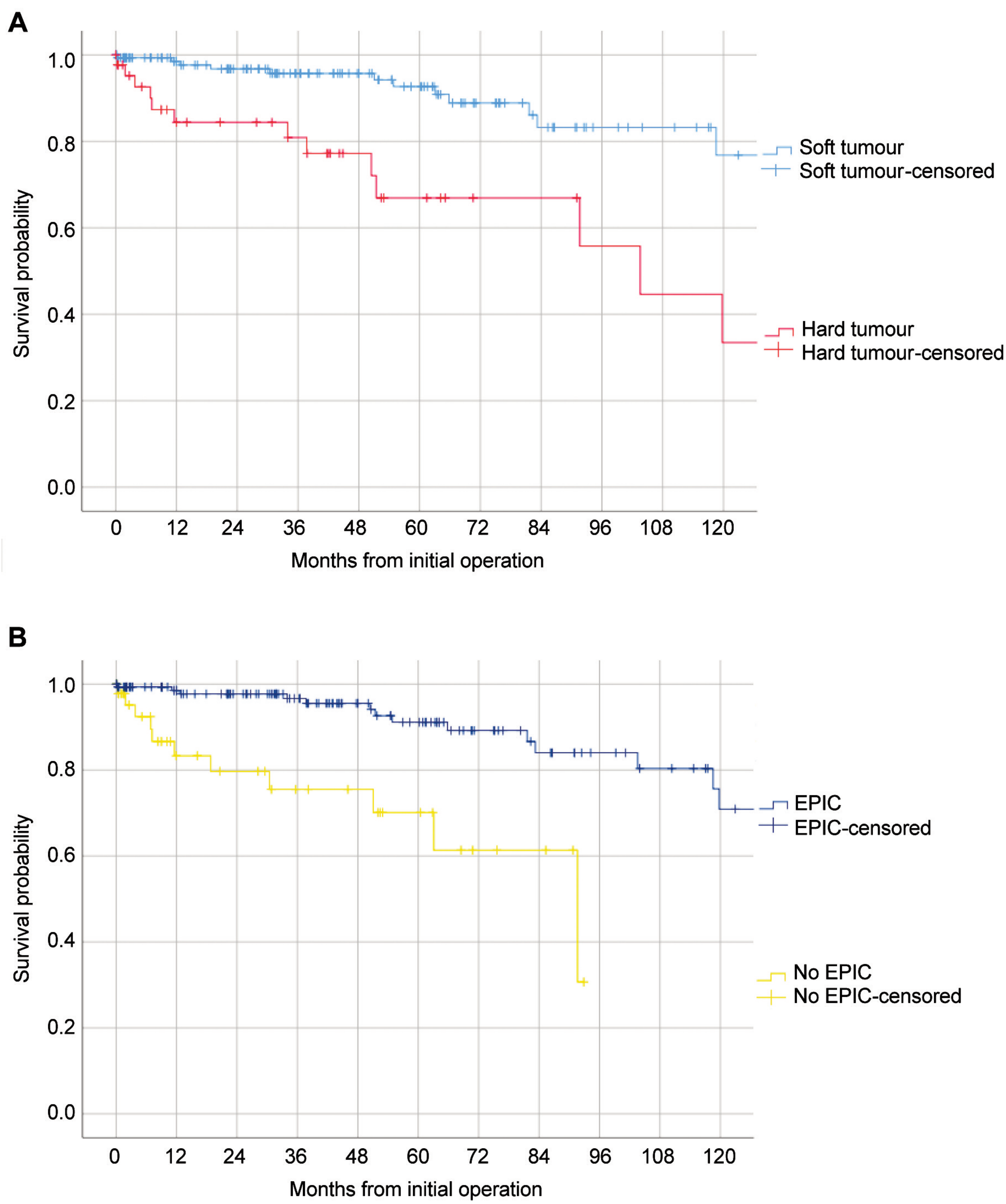

Figure 2. *Kaplan Meier survival curves stratified by tumour consistency and early postoperative intraperitoneal chemotherapy (EPIC) status. A. Kaplan Meier survival curve stratified by tumour consistency (soft and hard). B. Kaplan Meier survival curve stratified by EPIC status.*

morbidity and mortality. This is similar to appendiceal adenocarcinoma, where hard tumours were found to have a higher prevalence of signet cells and thus associated with worse prognosis (11). Whilst historically DPAM is often associated with higher OS compared to other gastrointestinal cancers with peritoneal metastases, a comparison of macroscopically soft and hard tumour consistency demonstrates that hard tumours may behave more similarly to the aggressive pattern of disease evidenced in appendiceal adenocarcinoma or PMCA (1, 17, 18). The worse OS for

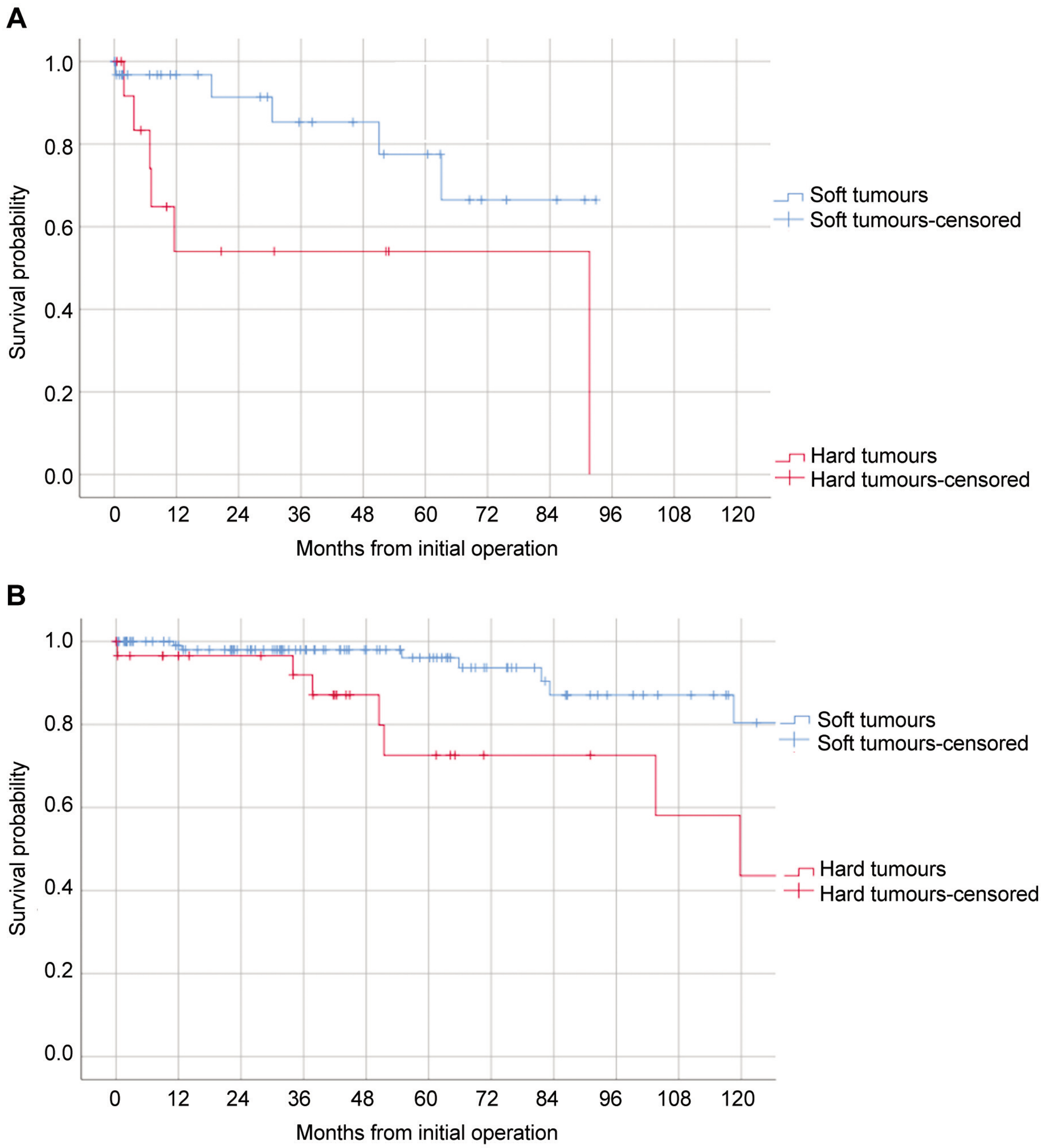

Figure 3. *Kaplan Meier survival curves of patients who did and did not receive early postoperative intraperitoneal chemotherapy (EPIC) stratified by tumour consistency. A. Survival of EPIC patients compared by tumour consistency. B. Survival of patients who did not receive EPIC compared by tumour consistency.*

hard DPAM may be attributed to differences in tumour biology and poorer loco-regional chemotherapy penetration through tumour mucin.

In DPAM there is significant intraoperative heterogeneity in terms of macroscopic appearance and consistency. Many patients with DPAM present with pools of soft mucinous ascites known as "jelly belly", whilst others demonstrate macroscopically firmer tumour nodules and hard mucin deposits. Tumour consistency in PMP is thought to be a function of percentage of water content and sialic acid. Laboratory analysis performed on the mucin produced by low grade appendiceal tumours demonstrated a 70% difference in sialic acid content between soft and hard mucin (19). Furthermore, differences in mucin gene expression have been

Table IV. *Survival probability comparing soft and hard tumours stratified by those who received early postoperative intraperitoneal chemotherapy (EPIC).*

Soft tumours	Survival probability for all soft tumours	Survival probability for soft tumours with EPIC	Survival probability for soft tumours without EPIC
12 months	0.98	0.98	0.91
36 months	0.96	0.98	0.85
60 months	0.89	0.94	0.66
Hard tumours	Survival probability for all hard tumours	Survival probability for hard tumours with EPIC	Survival probability for hard tumours without EPIC
12 months	0.85	0.96	0.58
36 months	0.77	0.86	0.58
60 months	0.66	0.72	0.58

observed, with harder tumours expressing a higher percentage of the MUC2 protein (19, 20). In colorectal cancer, MUC2 gene expression is found to produce a protective mucin layer that decreases the ability of HIPEC to penetrate tumour cells, rendering it less effective (21). Therefore, the difference in mucin gene expression may influence both tumour consistency and the effect of intraperitoneal chemotherapy. Currently, the importance of molecular gene expression for low grade appendiceal tumours is still largely unknown, as well as their relationship and implications on tumour pathobiology. Along these lines, a recent study investigating tumour microenvironments and metastatic potential found histological desmoplastic reactions (DR) influenced prognosis for metastatic colorectal cancers. Immature DR contained keloid-like collagen and demonstrated worse OS compared to mature DR with fine collagen fibres (22). Although DR is yet to be associated with tumour consistency, perhaps tumours with keloid-like collagen result in "harder" macroscopic consistency. Similarly, increased tumour stiffness in hepatocellular carcinomas is associated with reduced recurrence-free survival, suggesting greater tumor invasiveness (23). Both tumour stiffness and DR are yet to be investigated in appendiceal tumours and represent areas worthy of further investigation, as these molecular features and their relationship with tumour consistency can potentially influence treatment and OS.

The evaluation of local intraperitoneal chemotherapy on OS for different tumour consistencies was a key aim of our study. We have data demonstrating that hard mucinous tumours are poorly penetrated by intraperitoneal chemotherapy (data yet to be published). It is proposed that harder mucin forms a tough protective barrier around the tumour cells. This theory is reflected in the outcomes of this study which demonstrated better OS in soft tumours after CRS and HIPEC. As such, we have been investigating the use of a novel drug combination, Bromelain with N-Acetylcysteine, to synergically enhance the effect of chemotherapy by potentially "softening" these tumours (24). The use of Bromelain and N-acetylcysteine as a mucolytic agent with *in vitro* colorectal cell models is able to disintegrate mucin of both soft and hard consistency (20). We foresee the use of this drug combination to potentially disintegrate harder tumours and sensitise tumour cells to intraperitoneal chemotherapy and possible achieve similar outcomes found in soft tumours. These laboratory results are in progress and the application, efficacy and safety in patients are yet to be established. This is an ongoing key area of our unit's research.

Interestingly, our subgroup analysis found both soft and hard tumours resulted in longer OS when EPIC was given. The use of EPIC in the last decade has fallen out of favour at several centres due to concerns of increased morbidity, complications, and prolonged hospitalisation (25-27). We have previously demonstrated improved outcomes with EPIC in low grade appendiceal tumours with no significant differences in mortality or morbidity (28). Similarly, for other histological types of appendiceal PMP, Fung *et al*. reported a survival improvement for patients who received EPIC compared to those who did not, with 80.2% OS at 5-years compared to 76.4%, respectively (25). The results of the upcoming ICARus randomised trial comparing HIPEC and EPIC will provide more clarity on the role of EPIC in peritoneal malignancy (ICARus trial NCT01815359). In the meantime, we stress the merit of EPIC in all patients with DPAM, and especially those with hard tumours given the significant survival improvement found in our study (5-year OS 58% *vs*. 72%).

There are several limitations in this study. As a retrospective review, our results may have a selection bias. The macroscopic assessment of tumours was subjective; however, the majority were classified by a single surgeon. To date there is no practical intraoperative tool to objectively measure tumour consistency. There were several factors that limited patients from receiving EPIC including preoperative comorbidities, intraoperative complications, and immediate post-operative clinical conditions. These factors were not adjusted in this study and are a significant confounding factor in comparing the outcomes of EPIC in different tumour consistencies.

Conclusion

This study demonstrates a significant difference in tumour response to CRS and HIPEC based upon macroscopic features of DPAM. Further histological analysis and molecular studies are needed to explain the cellular differences between soft and hard tumours. Macroscopically soft tumours have improved OS, lower morbidity, mortality and reduced ICU and hospital stay over hard tumours. Thus, the assessment of tumour consistency can help guide intraoperative and postoperative clinical decision making and prognostication. Furthermore, the use of EPIC was found to be beneficial for both soft and hard tumours and therefore should be advocated for all patients with DPAM undergoing CRS and HIPEC.

Conflicts of Interest

David L. Morris is one of the inventors of Bromelain and N-Acetylcysteine (BromAc) and owns stock in the company Mucpharm pty ltd, Sydney, Australia.

Authors' Contributions

EC designed the study and the analysis method, collected data, performed data analysis, developed tables and figures, and wrote the manuscript. RS collected data and wrote the manuscript. JM collected data, developed tables and figures, and wrote the manuscript. JK wrote the manuscript. KC designed the analysis and project idea. NA conceived and developed the study and analysis. DLM conceived and conceptualised this study and wrote the manuscript.

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