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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Pleuropulmonary Recurrence Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemoperfusion for Appendiceal Pseudomyxoma Peritonei

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ABSTRACT

Background. The aim of this study was to identify factors associated with pleuropulmonary disease recurrence following cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC) for appendiceal pseudomyxoma peritonei (PMP) and to evaluate the oncologic impact of pleuropulmonary disease recurrence compared with isolated peritoneal recurrence.

Methods. From a prospective database, we identified patients who developed pleuropulmonary recurrence, isolated peritoneal recurrence, or no recurrence following CRS/HIPEC for appendiceal PMP. Clinicopathologic, perioperative, and oncologic data associated with the index CRS/HIPEC procedure were reviewed. The Kaplan–Meier method was used to estimate survival. Multivariate analyses identified associations with recurrence and survival.

Results. Of 382 patients undergoing CRS/HIPEC, 61 (16%) developed pleuropulmonary recurrence. Patients who developed a pleuropulmonary recurrence were more likely to have high-grade (American Joint Committee on Cancer [AJCC] grade 2/3) tumors (74% vs. 56%, $p = 0.02$) and increased operative blood loss (1651 vs. 1201 ml, $p = 0.05$) and were more likely to have undergone diaphragm stripping/resection (79% vs. 48%, $p < 0.01$) compared with patients with an abdominal recurrence. In a multivariate analysis, pleuropulmonary recurrence after CRS/HIPEC was associated with diaphragm stripping/resection, incomplete cytoreduction, and higher AJCC tumor grade. There was a trend towards reduced survival in patients with pleuropulmonary recurrence compared with patients with isolated peritoneal recurrence (median overall survival 45 vs. 53 months, $p = 0.87$).

Conclusion. Pleuropulmonary recurrence of appendiceal PMP following CRS/HIPEC is common and may negatively impact survival. Formal protocols for surveillance and therapeutic intervention need to be studied and implemented to improve oncologic outcomes.

Cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC), often in conjunction with systemic therapy, provides long-term survival benefit to patients with appendiceal pseudomyxoma peritonei (PMP).[1–3] Despite the efficacy of CRS/HIPEC, disease recurrence is common, with the risk of recurrence mainly associated with high burden of peritoneal disease (i.e. Peritoneal Cancer Index [PCI]), high-grade tumor histology, and inability to achieve complete cytoreduction at the time of CRS/HIPEC.[3–5] Disease recurrence remains isolated to the peritoneal cavity in most patients and the compressive and infiltrative nature of these tumors negatively impacts survival.[6,7]

Pleuropulmonary disease recurrence after CRS/HIPEC for appendiceal PMP is uncommon and has been described in several case reports and small single-institution series.[8–12] A variety of hypotheses have been proposed regarding mechanisms for pleuropulmonary metastasis,

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including direct diaphragm invasion, metastasis via congenital or acquired pleural–peritoneal communications, and lymphovascular dissemination.[9,12] Factors associated with pleuropulmonary recurrence are poorly understood and its prognostic significance remains unclear. A better understanding of the oncologic impact of a pleuropulmonary recurrence has the potential to improve perioperative management and postoperative surveillance. Identifying at-risk patients for a pleuropulmonary recurrence may alter treatment strategy at the time of the index operation.[13] In addition, earlier detection of a pleuropulmonary recurrence may afford potentially life-sustaining treatment options.[9,10,14]

In this study, we identified factors associated with a pleuropulmonary recurrence following CRS/HIPEC for appendiceal PMP, and evaluated the survival impact of pleuropulmonary disease recurrence in patients compared with patients with an isolated peritoneal recurrence.

METHODS

We performed a retrospective analysis of a prospective institutional database of patients with appendiceal PMP who underwent CRS/HIPEC between November 2000 and April 2017. Patients were stratified into three cohorts: (1) those with isolated peritoneal recurrence; (2) those with pleuropulmonary recurrence (irrespective of peritoneal recurrence); and (3) those without disease recurrence. Disease recurrence was determined based on radiographic findings (surveillance computed tomography [CT] or magnetic resonance imaging [MRI]) and by pathologic assessment when available. Pleural recurrences were characterized by pleural thickening and/or nodularity, and often with an associated pleural effusion. Pulmonary recurrences were characterized by soft tissue attenuated masses within the pulmonary parenchyma. In cases where a pleuropulmonary recurrence was in question, serial images were reviewed to identify progression of disease prior to defining a radiographic finding as a recurrence.

Demographic, clinicopathologic, perioperative, and oncologic data associated with the index CRS/HIPEC procedure were analyzed. We excluded patients with pleuropulmonary involvement at the time of initial diagnosis ($n = 6$), those without postoperative imaging ($n = 22$), and those with missing information regarding their index CRS/HIPEC procedure ($n = 7$). This study was approved by the University of Pittsburgh Institutional Review Board.

Patients with peritoneal metastases from an appendiceal mucinous neoplasm were presented at an institutional multidisciplinary tumor board and select patients were offered CRS and HIPEC. In patients with high-grade disease and extensive tumor involvement, neoadjuvant chemotherapy was offered. In patients with primarily abdominal disease who had diaphragm involvement discovered at the time of surgery, debulking of the abdomen/pelvis, peritonectomy, and, if needed, full-thickness resection of the diaphragmatic disease was performed and the defect closed prior to perfusion of the abdomen cavity only.

Disease burden at the time of surgery was quantified using the PCI. CRS was performed in accordance with the techniques described by Bao and Bartlett, and post-CRS residual disease was categorized as CC-0 (no residual macroscopic disease) or CC-1 (residual tumor nodule < 2.5 mm) resection; CC-2 (residual tumor nodule 2.5 mm–2.5 cm); or CC-3 (residual tumor nodule > 2.5 cm or confluent sheets of tumor).[15] An institutional protocol for HIPEC was initiated after CRS to maintain a target intraperitoneal tissue temperature of 42 °C. Postoperative complications were classified according to the Clavien–Dindo classification (grades 3–5 were considered major complications).[16] Appendiceal PMP histology was classified according to the American Joint Committee on Cancer (AJCC) grading system via low-grade (AJCC grade 1) or high-grade (AJCC grades 2/3) histology.[17]

Statistical Analysis

Clinicopathologic variables of patients with a pleuropulmonary recurrence, an abdominal recurrence, and those without a recurrence were compared using Chi square or Kruskal–Wallis tests when applicable. The univariate regression was first used to assess the outcome in relation to the available clinical and pathological characteristics in an exploratory fashion (Table 1). Based on the univariate analysis, significant differences were evaluated further in a multiple covariate model via stepwise procedures. Overall survival (OS) was calculated from the date of CRS/HIPEC to the date of death. For patients still alive at the time of analysis, follow-up was censored as of the date of last contact. Survival curves were estimated using the Kaplan–Meier method, and a generated log-rank test was used to compare survival outcomes in patients with and without a pleuropulmonary recurrence. Cox proportional hazards regression and multivariate linear regression analyses were performed to identify factors associated with survival. Statistical significance was set at $p < 0.05$ and all p values reported were two-sided. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

TABLE 1 Clinicopathologic and perioperative characteristics at CRS/HIPEC, stratified by site of subsequent disease recurrence [$n = 382$]

	Pleuropulmonary recurrence [$n = 61$]	Abdominal recurrence [$n = 140$]	No recurrence [$n = 181$]	Overall p value [PP vs. AP]
Age, years [mean (± SE)]	54.2 (11.32)	54.2 (12.39)	54.9 (11.19)	0.62 (0.71)
Karnofsky's performance [mean (± SE)]	87 (5.58)	89 (5.88)	91 (5.97)	
Preoperative albumin, mg/dl [mean (± SE)]	3.5 (0.81)	3.6 (0.76)	3.8 (0.65)	0.05 (0.64)
Preoperative CEA, ng/ml [mean (± SE)]	17.5 (28.07)	135.6 (629.79)	16.2 (43.09)	0.03 (0.12)
Preoperative CA19-9, U/ml [mean (± SE)]	236.7 (415.30)	492.9 (1465.14)	55.4 (203.02)	0.02 (0.68)
Prior chemotherapy [*n* (%)]	32 (52.5)	57 (40.7)	37 (20.4)	< 0.01 (0.14)
PCI [mean (± SE)]	23 (8.02)	21 (9.03)	16 (9.02)	< 0.01 (0.31)
CC score [*n* (%)]				< 0.01 (0.8)
CC-0	24 (39.3)	64 (46.0)	151 (84.8)	
CC-1	30 (49.2)	59 (42.4)	26 (14.6)	
CC-2	5 (8.2)	12 (8.6)	1 (0.6)	
CC-3	2 (3.3)	4 (2.9)	0 (0)	
Multiple peritonectomy [*n* (%)]	37 (60.7)	78 (55.7)	88 (48.6)	0.20 (0.54)
Diaphragm stripping/resection [*n* (%)]	48 (78.7)	67 (47.9)	79 (43.6)	< 0.01 (< 0.01)
Liver capsulectomy [*n* (%)]	7 (11.5)	8 (5.7)	19 (10.5)	0.24 (0.15)
Liver resection/RFA [*n* (%)]	10 (16.4)	16 (11.4)	18 (9.9)	0.42 (0.33)
Splenectomy [*n* (%)]	38 (62.3)	76 (54.3)	90 (49.7)	0.20 (0.22)
Operative time, min [mean (± SE)]	585 (178.1)	559 (160.8)	458 (147.7)	< 0.01 (0.42)
Estimated blood loss, ml [mean (± SE)]	1651 (1520)	1201 (1260)	692 (790)	< 0.01 (0.05)
AJCC classification [*n* (%)]				< 0.01 (0.02)
Grade G1	16 (26.2)	61 (43.9)	134 (74.4)	
Grade G2	29 (47.5)	39 (28.1)	34 (18.9)	
Grade G3	16 (26.2)	39 (28.1)	12 (6.7)	
Major (Clavien–Dindo grades 3–5) postoperative morbidity [*n* (%)]	22 (36.0)	38 (27.1)	29 (16.0)	< 0.01 (0.24)
Length of stay, days [mean (± SE)]	24.52 (57.5)	20.0 (30.9)	15.0 (28.4)	< 0.01 (0.92)

Overall p-values are shown in the last column, with p-values from a post hoc comparison of PP versus AP shown in parentheses

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *PP* pleuropulmonary recurrence, *AP* abdominal recurrence, *SE* standard error, *CEA* carcinoembryonic antigen, *CA19-9* cancer antigen 19-9, *PCI* Peritoneal Cancer Index, *CC* completeness of cytoreduction, *RFA* radiofrequency ablation, *AJCC* American Joint Committee on Cancer

RESULTS

Overall, 382 evaluable patients with appendiceal PMP underwent CRS/HIPEC. Following a median estimated follow-up period of 41 months (range 1–170), 140 (37%) patients developed disease recurrence in the peritoneal cavity alone (isolated peritoneal recurrence), while 61 patients (16%) developed pleuropulmonary disease recurrence (irrespective of peritoneal recurrence). Of the 61 patients with pleuropulmonary recurrence, 17 (5% overall) had pleural metastases only, 24 (6% overall) had pulmonary metastases only, and 20 (5% overall) had both pleural and pulmonary metastases.

Patients who developed pleuropulmonary recurrence demonstrated differences in clinicopathologic and perioperative features at the index CRS/HIPEC procedure when compared with those who developed isolated peritoneal recurrence only (Table 1). Patients who developed a pleuropulmonary recurrence were more likely to have high-grade (AJCC grade 2/3) tumors (74% vs. 56%) and increased operative blood loss (1651 vs. 1201 ml, $p = 0.05$), and were more likely to have undergone diaphragm stripping/resection (79% vs. 48%, $p < 0.01$). Although not statistically significant, there was a trend towards increased pleuropulmonary recurrences compared with isolated peritoneal recurrences in patients with higher disease burden at the time of CRS/HIPEC (PCI 23 vs. 21) and in those less likely to undergo CC-0 resection (39% vs. 46%) during the index CRS/HIPEC procedure. There was also a propensity towards patients with a pleuropulmonary recurrence having more extensive CRS in the upper abdomen, as demonstrated by the trend towards more

TABLE 2 Clinicopathologic variables associated with pleuropulmonary recurrence following CRS/HIPEC: multivariate analysis

Variable		*p* value	OR	95% CI
Karnofsky performance status	Yes	0.01	0.93	0.88–0.99
Diaphragm stripping	Yes	< 0.01	5.53	2.57–11.92
(referent: no)				
CC score	CC1	0.01	2.61	1.33–5.12
(referent: CC-0)	CC2		4.61	1.30–16.35
	CC3		2.35	0.23–23.59
AJCC classification	Grade 2	< 0.01	5.52	2.64–11.57
(referent: low-grade G1)	Grade 3		3.17	1.34–7.52
Major morbidity	Grade 3/4	0.134	1.70	0.8–3.4
(referent: grade 0–2)				

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *OR* odds ratio, *CI* confidence interval, *CC* completeness of cytoreduction, *AJCC* American Joint Committee on Cancer

frequent peritonectomy procedures (61% vs. 56%), liver capsulectomy (12% vs. 6%), liver resection/radiofrequency ablation (RFA; 16% vs. 11%), and splenectomy (62% vs. 54%). There was not a significant difference in the number of patients who received systemic chemotherapy prior to CRS/HIPEC in patients with a pleuropulmonary recurrence (53% vs. 41%) compared with those who developed an isolated peritoneal recurrence ($p = 0.14$).

Predictors of Pleuropulmonary Recurrence and Impact of Pleuropulmonary Recurrence on Survival

In a multivariate analysis, pleuropulmonary recurrence after CRS/HIPEC was associated with diaphragm stripping/resection at the time of surgery, incomplete cytoreduction, higher AJCC tumor grade, poor performance status, and major morbidity (Table 2). Of the patients who developed pleuropulmonary recurrence, 79% (48 patients) underwent diaphragm stripping/resection (i.e. diaphragm stripping in 27 patients, diaphragm resection in 21 patients) of one or both hemidiaphragms at the time of the index CRS/HIPEC procedure. Moreover, pleural recurrence occurred ipsilateral to the previous diaphragm stripping/resection in 82% of patients.

Patients with any disease recurrence (pleuropulmonary and/or peritoneal) had shorter OS compared with those without a recurrence ($p < 0.0001$). There was a trend towards reduced survival in patients with pleuropulmonary recurrence compared with patients with isolated peritoneal recurrence (median OS 45 vs. 53 months, $p = 0.87$) (Fig. 1). Furthermore, there was no difference in OS when patients were stratified by site of thoracic disease

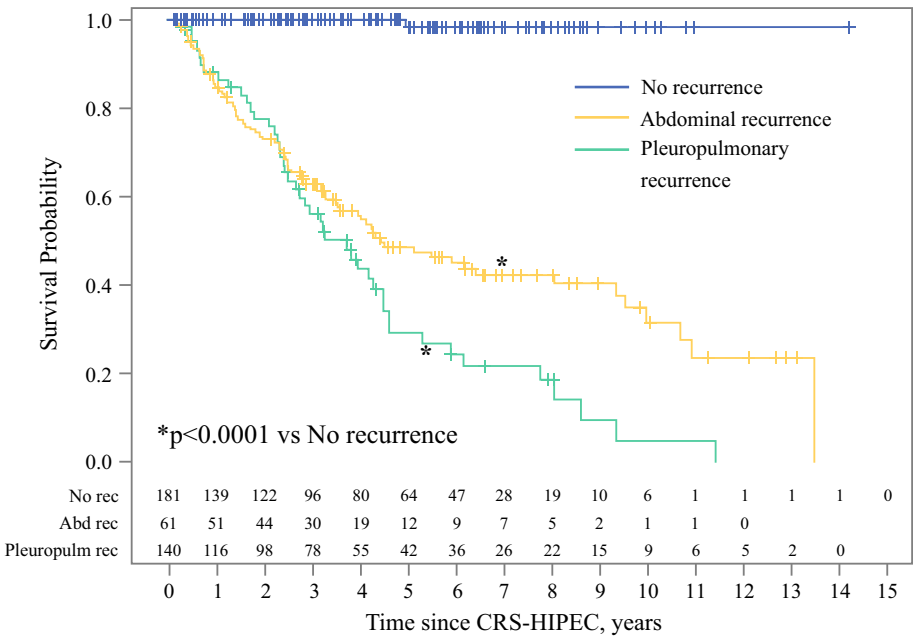

FIG. 1 Overall survival following CRS/HIPEC, stratified by site of disease recurrence. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *rec* recurrence, *Abd* abdominal, *pleuropulm* pleuropulmonary

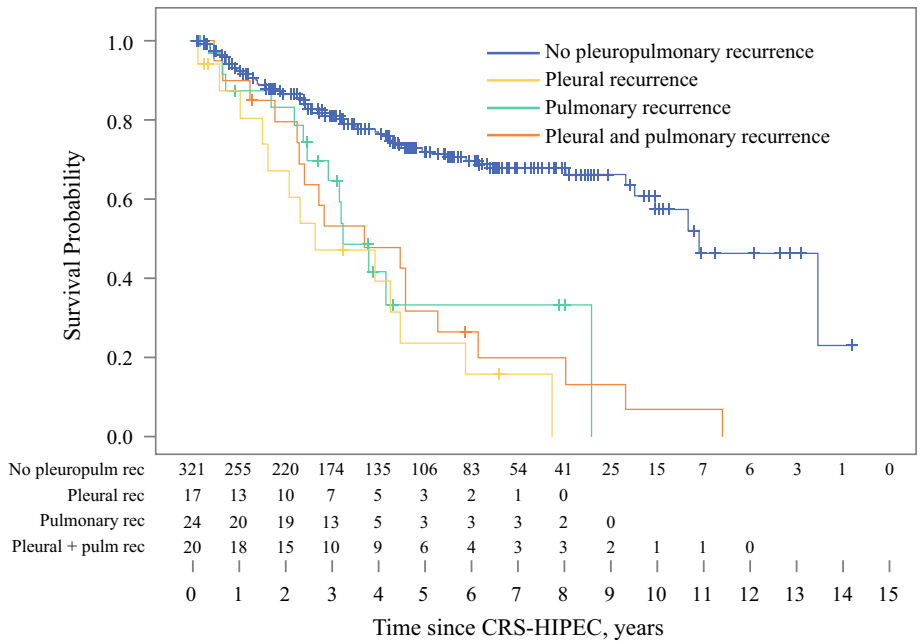

FIG. 2 Overall survival following CRS/HIPEC, stratified by site of thoracic disease recurrence. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *rec* recurrence, *pleuropulm* pleuropulmonary, *pulm* pulmonary

recurrence (pleural vs. pulmonary vs. both) (Fig. 2). Four patients who developed pleuropulmonary recurrence underwent subsequent thoracotomy with CRS/hyperthermic intrathoracic chemoperfusion (HITEC); one additional patient was treated with HITEC only. The median survival in these patients was 53.6 months (range 12.5–73.6), which is comparable with those with isolated peritoneal recurrence (53.4 months), and higher, but not statistically significant, compared with all patients with pleuropulmonary recurrence (44.5 months). In patients without a pleuropulmonary recurrence, 62 (19%) underwent more than one CRS/HIPEC procedure.

In a multivariate analysis, site of disease recurrence, completeness of cytoreduction, liver resection or RFA, AJCC tumor grade, KRAS mutation, and major morbidity were independent prognostic factors for OS following CRS/HIPEC (Table 3). Higher hazard ratios were associated with pleuropulmonary recurrence compared with

TABLE 3 Clinicopathologic variables associated with overall survival in patients following CRS/HIPEC: multivariate analysis

Variable		*p* value	HR	95% CI
Pleuropulmonary recurrence	Pleural	< 0.001	4.51	1.8–11.4
(referent: none)	Pulmonary		4.23	1.2–14.5
	Pleural and pulmonary		7.65	2.7–21.6
Peritoneal recurrence	Yes	0.021	1.93	1.1–3.4
(referent: no)				
CC (referent: CC-0)	CC-1	< 0.001	3.73	2.2–6.3
	CC-2		7.26	3.1–17.2
	CC-3		5.65	1.3–25.4
Liver resection/RFA	Yes	0.018	0.37	0.2–0.8
(referent: none)				
AJCC classification	Grade 2	< 0.001	7.77	4.2–14.4
(referent: low-grade G1)	Grade 3		17.34	9.1–32.9
KRAS status	Mutated	0.029	1.73	1.1–2.8
(referent: wild-type)				
Major morbidity	Grade 3/4	0.439	1.23	0.7–2.1
(referent grade 0–2)				

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemoperfusion, *HR* hazard ratio, *CI* confidence interval, *CC* completeness of cytoreduction, *RFA* radiofrequency ablation, *AJCC* American Joint Committee on Cancer

isolated peritoneal recurrence, suggesting an additional negative impact of pleuropulmonary recurrence over peritoneal recurrence alone.

DISCUSSION

We present the largest series to date of patients with pleuropulmonary recurrence of appendiceal PMP following CRS/HIPEC. Our data indicate that pleuropulmonary recurrence occurs more frequently than previously published and may be associated with reduced survival. Risk factors for pleuropulmonary recurrence following CRS/HIPEC include diaphragm stripping/resection at index surgery, incomplete cytoreduction, and high-grade tumors. Because potential treatment options are available for pleuropulmonary disease, formal protocols for surveillance and therapeutic intervention need to be studied and implemented to improve oncologic outcomes.[9,10,14]

The use of CRS/HIPEC to treat peritoneal metastases from appendiceal neoplasms has been shown to increase survival and is now widely accepted as the standard of care in select patients;[1] however, disease recurrence is common and is a significant challenge to achieving long-term cure. Previous studies have demonstrated that a significant burden of peritoneal disease, high-grade tumor histology, inability to achieve complete cytoreduction, and lymph node metastasis are all factors associated with peritoneal disease recurrence.[3–5] Pleural and pulmonary recurrences have been reported as rare events and have not been studied extensively. The incidence of pleuropulmonary recurrence was 5.4% (n = 23/426) in the largest published series over a 16-year period.[9] In the present study, the incidence of pleuropulmonary recurrence was much more common (16%) following CRS/HIPEC, but whether this reflects inherent differences in patient selection (e.g. PCI or tumor grade) or the true incidence of pleuropulmonary involvement, remains unknown. Similar to the study by Pestieau et al., the survival of patients with pleuropulmonary recurrence in the current study was associated with reduced survival.[9] With more than 1 of 10 patients being at risk, a heightened awareness of this phenomenon has important implications in treatment and surveillance strategies.

Identifying at-risk patients for pleuropulmonary recurrence may alter treatment strategies at the time of index CRS/HIPEC. Until now, the risk of pleuropulmonary recurrence in patients with a significant subdiaphragmatic peritoneal burden was unknown. Many centers have adopted simultaneous intraperitoneal and intrapleural chemoperfusion following diaphragm resection as a preventative measure to reduce thoracic recurrence.[13] While this practice may be associated with increased morbidity, and, in one series, mortality, there is some evidence to suggest that thoracoabdominal perfusion following diaphragm resection is safe and may reduce the risk of thoracic recurrence.[13,18,19] While none of the patients in the present series underwent thoracoabdominal perfusion at the time of their initial CRS/HIPEC, our review confirms an increased risk of pleuropulmonary recurrence in patients who undergo diaphragm stripping/resection. Accordingly, consideration should be given to thoracoabdominal perfusion in patients who require more diaphragm stripping/resection to remove peritoneal disease.

Patients at risk of pleuropulmonary recurrence may benefit from enhanced surveillance of the thoracic cavity. Multiple studies support repeat CRS/HIPEC for patients with peritoneal recurrence, and a growing body of evidence suggests that pulmonary metastectomy with or without pleural CRS and HITEC has the potential to improve outcomes in these patients.[8,10,19–22] In the study by Pestieau et al., 35% of patients who developed pleuropulmonary recurrence underwent thoracotomy and CRS.[9] In the subset of patients who underwent CRS/HITEC, 22% remained disease-free at the time of publication (range of 2–42 months). While the majority of operations performed for pleuropulmonary recurrence in the literature are palliative in nature, others are performed for curative intent, and disease-free intervals can be as high as 2–14 years.[8] In our study, four patients who developed pleuropulmonary recurrence underwent subsequent thoracotomy with CRS/HITEC; one additional patient was treated with HITEC only. The median survival in these patients was 53.6 months (range 12.5–73.6), which is comparable with those with isolated peritoneal recurrence (53.4 months) and higher than all patients with pleuropulmonary recurrence (44.5 months). Given the potential of regional therapy to improve outcomes in patients with a pleuropulmonary recurrence, efforts should be made to detect recurrences early on so that opportunities to intervene are not forgone.

The present study effectively identified variables associated with pleuropulmonary recurrence, including diaphragm stripping/resection at the time of index surgery, incomplete cytoreduction, and higher AJCC tumor grade. The ability to use these factors to prospectively identify at-risk patients and guide surveillance practices will require further investigation. There has been a trend towards using MRI of the abdomen due to its superior contrast resolution in the evaluation of mucinous tumors.[23–25] This is especially true in the surveillance of younger patients to minimize exposure to the radiation associated with frequent and repeated CT scans. In doing so, evaluation of the chest by high-resolution imaging is often forgone. While the diaphragms are frequently evaluated during abdominal MRI, pulmonary metastases could be missed, and 11% of patients in our study developed pulmonary recurrences.

Identifying and properly surveilling at-risk patients may afford early diagnosis of pleuropulmonary recurrences and affect the timing of management decisions in patient care.

Limitations

While these findings are novel, there are limitations to the study with which these results must be interpreted. Foremost, the definition of a pleuropulmonary recurrence was based on radiographic findings alone. While patients with pleuropulmonary recurrence in our study did not have subtle findings on surveillance CT scans, pathologic confirmation was not performed in all instances. Another limitation is inherent to the retrospective nature of the study, which may introduce bias. To this end, there is significant heterogeneity within each cohort of patients with tumor recurrence (peritoneal/pleuropulmonary recurrence cohorts) that may confound our findings. The biology and hence clinicopathologic factors associated with a pleural recurrence is likely very different than that of what is associated with a pulmonary recurrence, but remains unknown, and the low frequency with which each occurred in this study precludes any meaningful comparison of the clinicopathologic factors associated with one versus the other. With regard to the operative variables, the indications for performance of diaphragm stripping/resection and the degree of disease burden is difficult to ascertain retrospectively. As such, whether the pleuropulmonary recurrences observed in our study were a result of extensive diaphragmatic tumor burden at the time of CRS/HIPEC, due to iatrogenic tumor seeding of the thoracic cavity during surgery, or aggressive tumor biology, cannot be ascertained. Lastly, there may be other factors associated with the development of a pleuropulmonary recurrence that were not captured by chart review and were thus not included in the multivariate model.

The median OS in patients with a pleuropulmonary recurrence was 45 months, compared with 53 months in patients with an isolated peritoneal recurrence ($p = 0.87$). Because there is no comparison cohort of at-risk patients who only underwent observation, it is beyond the scope of this analysis to determine if patients who developed a pleuropulmonary recurrence derived a benefit from CRS/HIPEC. However, patient selection is of utmost importance and this should be taken into consideration when offering CRS/HIPEC to patients at risk for local and/or distant recurrence.

CONCLUSION

Pleuropulmonary recurrence of appendiceal PMP occurs more frequently than previously reported and may be associated with reduced survival. At-risk patients include those who undergo diaphragm stripping/resection at the time of CRS/HIPEC, those who undergo incomplete cytoreduction, and those with higher-grade tumors. Formal protocols for surveillance and therapeutic intervention need to be studied and implemented to improve oncologic outcomes.

AUTHOR'S CONTRIBUTION This study was designed and conceptualized by JDB and HAC; data were acquired by JDB, GCW, JMS, and LR; analysis and interpretation of the data was performed by JDB, YS, and HAC; and the manuscript was initially drafted by JDB and HAC, with critical revisions by GCW, JMS, YS, HLJ, JFP, MPH, AJZ, SAA, HJZ, and DLB.

DISCLOSURE Joal D. Beane, Gregory C. Wilson, Jeffrey M. Sutton, Yongli Shuai, Lekshmi Ramalingam, Heather L. Jones, James F. Pingpank II, Matthew P. Holtzman, Amer J. Zureikat, Steven A. Ahrendt, Herbert J. Zeh, David L. Bartlett, and Haroon A. Choudry have no conflicts of interest to declare.

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