

Splenectomy is an independent risk factor for poorer perioperative outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: an analysis of 936 procedures

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Background: There is a paucity of data on the impact of splenectomy on peri-operative outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). We report the largest series to date which addresses this topic.

Methods: Nine hundred and thirty six consecutive patients underwent CRS/HIPEC from 1996 to 2016 at a high-volume institution in Sydney, Australia. Of these, 418 (45%) underwent splenectomy. Peri-operative complications were graded according to the Clavien-Dindo Classification. The association of splenectomy with 19 peri-operative outcomes was assessed using univariate and multivariate analyses.

Results: In-hospital mortality was 1.8%. Patients undergoing splenectomy had a higher disease burden (peritoneal cancer index ≥ 17) (71% vs. 22%, $P < 0.001$) and underwent a longer operation (≥ 9 hours) (73% vs. 34%, $P < 0.001$). Even after accounting for confounding factors, splenectomy was independently associated with an increased risk of grade III/IV morbidity [relative risk (RR), 1.94; 95% confidence interval (CI), 1.29–2.91; $P = 0.01$], infective complications (RR, 1.63; 95% CI, 1.09–2.44; $P = 0.018$), pancreatic leak (RR, 5.2; 95% CI, 1.81–14.89, $P = 0.002$) and intra-abdominal collection (RR, 1.86; 95% CI, 1.23–2.84, $P = 0.004$). It was also an independent risk factor for long hospital stay (≥ 28 days) (RR, 1.98; 95% CI, 1.25–3.11; $P = 0.003$). Splenectomy was not associated with in-hospital mortality (RR, 1.68; 95% CI, 0.32–9.32, $P = 0.556$).

Conclusions: Splenectomy is an independent risk factor for poorer peri-operative outcomes. Minimizing the likelihood of inadvertent splenic injury through careful dissection and routine vaccination can improve outcomes.

Keywords: Splenectomy; morbidity; mortality; length of stay; hyperthermic; intraperitoneal; cytoreductive

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Introduction

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a potentially curative treatment for select patients with peritoneal carcinomatosis. This combined approach has consistently demonstrated improved survival outcomes across a variety of disease types including colorectal cancer, peritoneal mesothelioma, and peritoneal mesothelioma (1-3). There is

randomized evidence demonstrating the superiority of CRS-HIPEC for colorectal cancer peritoneal carcinomatosis (2).

This treatment, however, has been associated with a high rate of perioperative mortality and morbidity compared to other gastrointestinal surgeries. A critical appraisal of the literature shows that in-hospital mortality varies widely across institutions between 0–17% (4). In high volume institutions, however, CRS/HIPEC is relatively safe with a

reported mortality of 0–5.8% (4). The rate of grade III/IV morbidity ranges from 12–52% in high volume centers (4–6). Given the need to optimize outcomes and improve patient selection several studies have identified factors which are associated with a poorer peri-operative outcomes. It is widely acknowledged that the volume of disease, extent of cytoreduction and length of operation are associated with a poorer peri-operative outcome (5–7). Few studies, however, have evaluated the impact of specific procedures on peri-operative outcomes.

Splenectomy is relatively common procedure during CRS/HIPEC performed in up to 50% of patients in high-volume institutions (5,8). It is usually performed due to tumor involvement of the spleen or iatrogenic trauma during dissection in the left upper quadrant. Inadvertent splenectomy during other gastrointestinal surgical procedures has been associated with a higher rate of perioperative morbidity and infections complications (9–12). Moreover, splenectomy may compromise long term survival outcomes and increase the risk of developing new solid and hematologic malignancies (10,13,14). To our knowledge, only one small study has addressed the impact of splenectomy on peri-operative outcomes after CRS/HIPEC (8). The primary aim of this study was to evaluate the independent impact of splenectomy on mortality and morbidity outcomes in a large number of patients treated at a high-volume institution by a single surgeon.

Methods

The institutional review committee deems retrospective analysis of the prospectively maintained St George Hospital Peritoneal Malignancy Program Dataset to be of low-negligible risk. This is because they involve a review of de-identified data which patients had agreed to provide prior to surgery. From September 1996 to December 2015, 936 consecutive patients who underwent CRS/HIPEC by a single surgical team at St George Hospital, Sydney, Australia, were identified from a prospective database and analyzed. Selection of suitable patients for this procedure was based on the extent of disease and ability to achieve a complete cytoreduction, performance status and comorbidities. Patients who had a splenectomy during their cytoreductive procedure were identified. A case control group of similar patients, without splenectomy, was selected from the same database.

The extent of peritoneal disease was calculated and recorded using the peritoneal carcinomatosis index (PCI) as

described by Jacquet and Sugarbaker (15). CRS/HIPEC was performed according to the Sugarbaker technique (16). The completeness of cytoreduction was recorded as previously described (15).

Operation reports were analyzed for the number of operative procedures performed. Demographic data, tumor characteristics, operative and postoperative details were extracted from the database and postoperative complications were graded according to the Clavien-Dindo Classification (17). All statistical analyses were performed using SPSS® (Windows Version 22, IBM Corporation, New York, USA). Patient characteristics were reported using frequency and descriptive analyses. Comparison of normally distributed variables was performed using the unpaired *t*-test. Categorical variables were analyzed using the Chi-square test (or Fisher's exact test when conditions for Chi square were not fulfilled). Hospital mortality was defined as death that occurred during the same admission for CRS/HIPEC. Univariate analysis for complications was performed using Chi square tests or Fisher's exact test, where appropriate. Multivariate analyses were performed using a binary logistic regression model. The significance level was set at 0.05.

Results

Patient characteristics

A thorough summary of patient characteristics is provided in *Table 1*. Overall, 418 (45%) patients underwent splenectomy (Group 1). Five hundred and eighteen (55%) patients did not undergo splenectomy (Group 2). Five hundred and twenty six (56%) patients were female. The mean age of patients at the time of surgery was 53.9 ± 13.3 (range, 14–86) years. The mean PCI of patients was 17.0 ± 11.5 (range, 0–39). The histopathology of the primary tumor was colorectal cancer in 265 (28%) patients, diffuse peritoneal adenomucinosis (DPAM) in 249 (27%), peritoneal mesothelioma in 82 (9%), appendiceal cancer in 234 (25%), ovarian cancer in 43 (5%) and other malignancies in 63 (7%). The completeness of cytoreduction was CC0 in 619 (67%) patients, CC1 in 267 (29%), CC2 in 41 (4%) and CC3 in 3 (0%). The mean number of peritonectomy procedures performed was 3.88 ± 1.82 (0–6).

Table 1 demonstrates the differences in the baseline characteristics between patients in Group 1 and 2, respectively. Patients in Group 1 generally had a higher PCI ($P < 0.001$) and consequently underwent longer procedures

Table 1 Clinicopathological and treatment related factors, stratified by group

Clinicopathological and treatment-related factors	No splenectomy (Group 2)	Splenectomy (Group 1)	P value
Total (n)	518	418	–
Age at time of surgery (years)			0.55
Mean ± SD (range)		53.9±13.3 [14–86]	
<54	255	197	
≥54	263	221	
Gender			0.90
Female	290	236	
Male	228	182	
PCI			<0.001
Mean ± SD (range)		17.0±11.5 [0–39]	
<17	404	123	
≥17	114	295	
Completeness of cytoreduction			<0.001
CC0	411	212	
CC1/2/3	107	206	
Primary histopathology			<0.001
Colorectal cancer	206	59	
DPAM	105	144	
Peritoneal mesothelioma	46	36	
Appendiceal cancer	98	136	
Other	45	18	
Ovarian cancer	18	25	
Operation length (hours)			<0.001
Mean ± SD (range)		8.7±3.0 [2–24]	
<9	344	110	
≥9	174	307	
RBC transfusion			<0.001
Mean ± SD (range)		5.0±6.8 [0–47]	
<5	408	190	
≥5	110	226	
Partial hepatectomy			0.35
No	438	362	
Yes	80	55	
Partial gastrectomy			<0.001
No	497	359	
Yes	20	57	

Table 1 (continued)

Table 1 (continued)

Clinicopathological and treatment-related factors	No Splenectomy (Group 2)	Splenectomy (Group 1)	P value
Diaphragm strip			<0.001
None	358	50	
Right only	109	59	
Left only	9	25	
Bilateral	42	284	
Colonic resection			<0.001
No	186	71	
Yes	332	346	
Number of peritonectomy procedures			<0.001
Mean ± SD (range)		3.88±1.82 [0–6]	
<4	342	41	
≥4	177	376	
Early postoperative intraperitoneal chemotherapy			0.019
No	324	229	
Yes	190	185	
Pelvic peritonectomy			<0.001
No	173	41	
Yes	345	377	
Greater omentectomy			<0.001
No	202	107	
Yes	316	311	
Cholecystectomy			<0.001
No	290	85	
Yes	228	332	
Stoma formation			<0.001
No	338	186	
Yes	180	231	
Ureteric procedure			0.81
No	472	384	
Yes	43	32	
Small bowel resection			0.26
No	298	256	
Yes	220	161	
Hysterectomy			0.56
No	454	358	
Yes	64	57	
ASA score			0.123
1 or 2	172	120	
3 or 4	278	346	
Missing	120		

PCI, Peritoneal cancer index; DPAM, diffuse peritoneal adenomucinosis; ASA, American Society of Anesthesiologists.

($P < 0.001$) with more peritonectomy procedures performed ($P < 0.001$). Group 1 patients were more likely to undergo other procedures including colonic resection ($P < 0.001$), partial gastrectomy ($P < 0.001$) and diaphragmatic stripping ($P < 0.001$).

Impact of splenectomy on perioperative outcomes

The mortality rate in the entire series was 1.8%. *Table 2* stratifies perioperative outcomes based on group. On univariate analysis, patients in Group 1 were more likely to develop infective complications (46% *vs.* 30%, $P < 0.001$), pancreatic leak (11% *vs.* 2%, $P < 0.001$), pneumonia (11% *vs.* 5%, $P < 0.001$), pneumothorax (13% *vs.* 5%, $P < 0.001$), perforated viscus (5% *vs.* 2%, $P < 0.001$), intra-abdominal collection (49% *vs.* 27%, $P < 0.001$), bleeding (11% *vs.* 4%, $P < 0.001$), digestive fistula (16% *vs.* 8%, $P < 0.001$) and sepsis (23% *vs.* 13%, $P < 0.001$). Group 1 patients were more likely overall to develop grade III/IV morbidity (57% *vs.* 30%, $P < 0.001$). They were more likely to have a long hospital stay (≥ 28 days) (45% *vs.* 21%, $P < 0.001$) and long intensive care unit (ICU) stay (≥ 4 days) (37% *vs.* 18%, $P < 0.001$). Group 1 was not associated with in-hospital mortality (3% *vs.* 1%, $P = 0.138$).

Table 3 summarizes the results of multivariate analysis evaluating the impact of splenectomy on peri-operative outcomes. Splenectomy was independently associated with a higher risk of infective complications [relative risk (RR), 1.63; 95% confidence interval (CI), 1.09–2.44; $P = 0.018$], pancreatic leak (RR, 5.2; 95% CI, 1.81–14.89, $P = 0.002$), intra-abdominal collection (RR, 1.86; 95% CI, 1.23–2.84, $P = 0.004$), and grade III/IV morbidity (RR, 1.94; 95% CI, 1.29–2.91; $P = 0.01$). It was also an independent risk factor for long hospital stay (≥ 28 days) (RR, 1.98; 95% CI, 1.25–3.11; $P = 0.003$) and long ICU stay (≥ 4 days) (RR, 2.18; 95% CI, 1.39–3.44, $P = 0.001$).

Discussion

Our study demonstrates that splenectomy is an independent risk factor for poorer peri-operative outcome after CRS/HIPEC. Even after accounting for confounding factors, patients undergoing splenectomy were twice as likely to develop grade III/IV morbidity (57% *vs.* 30%; RR, 1.94; $P < 0.001$). This could be attributed in part to the fact that these patients were 63% more likely to develop infection and 86% more likely to develop an intra-abdominal collection.

Splenectomy was also associated with a fivefold increase in the risk of pancreatic leak (11% *vs.* 2%, $P = 0.002$). This reflects the fact that splenectomy involves extensive dissection around the pancreatic tail increasing the incidence of inadvertent pancreatic injury. The poorer peri-operative outcomes meant that splenectomy patients were twice as likely to have a prolonged hospital stay (≥ 28 days, $P = 0.003$) and ICU stay (≥ 4 days, $P = 0.001$). Reassuringly, however, splenectomy was not associated with an increased risk of in-hospital mortality (3% *vs.* 1%, $P = 0.556$).

Some of the differences observed reflect the significant differences between the two groups. Indeed, of the 19 peri-operative variables assessed, splenectomy was associated with an increased incidence of 15 on univariate analysis but only 6 on multivariate analysis. Consistent with previous series, we demonstrated that splenectomy patients have a higher disease burden and require a more extensive cytoreduction (8). In this series, 71% of patients undergoing splenectomy had a PCI ≥ 17 compared to only 22% in those who did not. Splenectomy patients were more likely to have undergone procedures such as diaphragmatic stripping ($P < 0.001$), colonic resection ($P < 0.001$) and stoma formation ($P < 0.001$). Operation length, a surrogate marker for surgical complexity was significantly longer in the splenectomy group ($P < 0.001$). Moreover, these patients were more likely to intra-operatively receive massive blood transfusion (≥ 5 units, $P < 0.001$). Undoubtedly, splenectomy patients constitute a group with higher disease burden. Nevertheless, our data suggests that the addition of splenectomy to long and complex procedures such as CRS/HIPEC further increases morbidity risk.

Only one small study has addressed the impact of splenectomy on peri-operative outcomes after CRS/HIPEC. Dagbert and colleagues (8) performed a case control study of 61 patients who underwent CRS/HIPEC over a 3-year period; 30 (49%) had a splenectomy. The authors demonstrated that patients in the splenectomy group experienced more grade 3–4 complications than those in the control group (59% *vs.* 35.9%, $P = 0.041$) as well as more pulmonary complications (41% *vs.* 7.7%, $P = 0.006$). Splenectomy was the only predictor of grade 3–4 complications on multivariate analysis (risk ratio, 2.57; 95% CI, 1.03–6.40). There was no difference in mortality between the two groups. The authors did not show an independent association of splenectomy with infective complications; this, however, may reflect the small number of patients in the study.

Unplanned splenectomy has been consistently

Table 2 Peri-operative outcomes after CRS/HIPEC, stratified by group

Peri-operative outcomes	No splenectomy (Group 2)	Splenectomy (Group 1)	P value (univariate)
Total (n)	518	418	–
Infective complication			<0.001
No	364	226	
Yes	154	191	
Heart problem			0.124
No	481	375	
Yes	37	42	
Small bowel obstruction			0.728
No	498	403	
Yes	20	14	
Return to theatre			<0.001
No	467	329	
Yes	52	88	
Pancreatic leak			<0.001
No	508	370	
Yes	10	47	
Renal impairment			0.153
No	508	402	
Yes	10	15	
Pneumonia			<0.001
No	493	373	
Yes	25	44	
Pneumothorax			<0.001
No	492	364	
Yes	26	53	
Perforated viscus			0.009
No	510	398	
Yes	8	19	
Intra-abdominal collection			<0.001
No	376	211	
Yes	142	206	
Bleeding			<0.001
No	498	373	
Yes	21	44	

Table 2 (continued)

Table 2 (continued)

Peri-operative outcomes	No splenectomy (Group 2)	Splenectomy (Group 1)	P value (univariate)
Pleural effusion			<0.001
No	418	275	
Yes	100	142	
Digestive fistula			<0.001
No	475	351	
Yes	44	66	
Ileus			0.836
No	458	371	
Yes	60	46	
Sepsis			<0.001
No	450	322	
Yes	68	95	
Grade III/IV morbidity			<0.001
No	365	180	
Yes	154	237	
Length of hospital stay (days)			<0.001
Mean ± SD (all patients)		28.03±25.65	
<28	411	227	
≥28	107	189	
Length of ICU stay (days)			<0.001
Mean ± SD (all patients)		4.16±7.75	
<4	426	262	
≥4	92	154	
In-hospital mortality			0.138
No	512	407	
Yes	6	11	

associated with poorer perioperative outcomes in patients undergoing other types of intra-abdominal surgery. Mettke and colleagues (9) performed a prospective multicentre study of 46,682 patients who underwent resection for colorectal carcinoma between 2000 and 2004. Of these, 640 (1.4%) suffered an iatrogenic splenic injury during surgery necessitating either removal or repair. The authors demonstrated that splenectomy increased both morbidity (47.2% *vs.* 36.5%, $P=0.003$) and mortality (11.8% *vs.*

3.1%, $P<0.001$). Anastomotic leaks requiring surgery were observed most frequently following splenectomy (7.9%) but this was significantly lower following spleen preservation (3.3%, $P=0.003$). An association of splenectomy with impaired anastomotic healing has been reported in animal studies and may explain the increased risk of peri-operative morbidity that we observed (18). Wang and colleagues (10) evaluated 4,323 patients who underwent nephrectomy at Mayo clinic between 1992 and 2008; 33 (0.8%) had an

Table 3 Multivariate analysis on the impact of splenectomy on peri-operative outcomes after CRS/HIPEC

Peri-operative outcomes	RR	95% CI	P value (multivariate)
Infective complication	1.63	1.09–2.44	0.018**
Heart problem	1.01	0.51–2.03	0.968
Small bowel obstruction	0.83	0.30–2.32	0.725
Return to theatre	1.56	0.90–2.72	0.115
Pancreatic leak	5.20	1.81–14.89	0.002**
Renal impairment	1.70	0.52–5.53	0.380
Pneumonia	1.69	0.81–3.52	0.159
Pneumothorax	0.76	0.38–1.49	0.415
Perforated viscus	2.52	0.69–9.28	0.164
Intra-abdominal collection	1.86	1.23–2.84	0.004**
Bleeding	1.55	0.73–3.29	0.257
Pleural effusion	1.47	0.94–2.31	0.091
Digestive fistula	1.46	0.74 - 2.88	0.278
Ileus	0.85	0.46–1.59	0.608
Sepsis	1.41	0.84–2.36	0.199
Grade III/IV morbidity	1.94	1.29–2.91	0.01**
Length of hospital stay \geq 28 days	1.98	1.25–3.11	0.003**
Length of ICU stay \geq 4 days	2.18	1.39–3.44	0.001**
In-hospital mortality	1.67	0.30–9.32	0.556

** , P<0.05. RR, relative risk .

unplanned splenectomy. Consistent with the results of our study, patients with unplanned splenectomy had longer operative times (205 *vs.* 171 min; P=0.02), higher estimated blood loss (1.3 *vs.* 0.3 L; P=0.001), longer length of stay (median 7 *vs.* 5 days; P=0.03) and a greater incidence of peri-operative morbidity (RR 5.3; P=0.002). Similar outcomes have been reported for esophageal and gastric cancer surgery (11,12).

There is an immunological basis for the increased morbidity observed in patients undergoing splenectomy. The spleen functions as a phagocytic filter which removes damaged cells, eliminates blood-borne microbes and also producing antibiotics (19). Consistent with the results of this study, there is a definitive association between asplenia and increased morbidity and mortality from infectious etiologies (20). Overwhelming postsplenectomy sepsis (OPSS) is a significant concern in the asplenic patient and occurs in in 0.05% to 2% of splenectomized patients (21). This is related to the increased risk of infection by

encapsulated organisms, most commonly by Streptococcus pneumonia, both also haemophilus influenza and Neisseria meningitides (22). This has led to the knowledge that splenectomized patients should be vaccinated to decrease the risk of OPSS due to organisms (19). In our institution, all patients, whenever possible, are vaccinated 2 weeks before the operation in order to allow patients to create antibodies and prevent OPSS.

In the context of CRS/HIPEC, splenectomy is most commonly performed for tumor implantation. In this case, spleen preservation is only possible when there is minor splenic involvement, particularly in mucinous tumors. Partial spleen capsulectomy can be effectively performed for limited disease (8). Iatrogenic splenic injury is another common cause of splenectomy. As discussed by Dagbert and colleagues (8), intraoperative splenic injury may be the result of inferior pole avulsion during mobilization of the splenic flexure of the colon or from aggressive retractor placement on the greater omentum during completion

omentectomy. Limiting traction on the omentum is pertinent to reducing the risk of inadvertent splenic injury. Moreover, careful dissection when undertaking adjunct procedures such as stripping of the left diaphragm maximizes the likelihood of spleen conservation. When inadvertent splenic injury occurs, there are some potential therapeutic options. Electrocautery can be used but it may exacerbate the existing injury. There have been promising reports on the use of topical fibrin sealant and surgical adhesive to the laceration site (10,23). These warrant further exploration in the setting of CRS/HIPEC. Splenorrhaphy, utilizing pledgeted sutures, mesh and topical hemostatic agents has been used to good effect in the trauma setting (24). Nevertheless, splenic repair is not always successful and many patients initially considered suitable for spleen salvage will subsequently require splenectomy (25).

Our study is by far the largest to evaluate the impact of splenectomy on outcomes after CRS/HIPEC. Nevertheless, it has several limitations. Firstly, it is an observational, retrospective study from a single high volume institution. The results from this study may not necessarily translate into those observed at other centers. Moreover, limitations inherent to a retrospective study design also apply to this study. Secondly, potential confounding from unknown variables may have affected the analyses. In particular, it must be noted that patients undergoing splenectomy generally underwent a more extensive cytoreductive procedure. Although we accounted for adjunct procedures and the extent of cytoreduction, unknown variables could have influenced outcomes. Thirdly, whilst this is by far the largest study to examine the impact of splenectomy on peri-operative outcomes, it may not be sufficiently powered to demonstrate an association with low event rate complications such as in-hospital mortality. Nevertheless, this study shows with significant conviction that splenectomy independently confers a poorer peri-operative outcome.

In conclusion, splenectomy is an independent risk factor for poorer peri-operative outcomes including grade III/IV complications, infection and pancreatic leak. Minimizing the likelihood of inadvertent splenic injury through careful dissection and routine vaccination of CRS/HIPEC patients prior to surgery can improve outcomes. Spleen-conserving surgery in the presence of limited metastatic involvement should also be considered.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical statement: The study was approved by institutional ethics committee of St George Hospital.

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