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PCI is Not Predictive of Survival After Complete CRS/HIPEC in Peritoneal Dissemination from High-Grade Appendiceal Primaries

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Abstract

Background—Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a treatment option in patients with carcinomatosis from high-grade appendiceal (HGA) primaries. It is unknown if there is a Peritoneal Carcinomatosis Index (PCI) upper limit above which a complete CRS/HIPEC does not assure long-term survival.

Methods—Retrospective analysis from three centers was performed. The PCI was used to grade volume of disease. Survival in relation to PCI was studied on patients with complete cytoreduction.

Results—Overall, 521 HGA patients underwent CRS/HIPEC from 1993 to 2015, with complete CRS being achieved in 50% (260/622). Mean PCI was 14.8 (standard deviation 8.7, range 0–36). Median survival for the complete CRS cohort was 6.1 years, while 5- and 10-year survival was 51.7% (standard error [SE] 4.6) and 36.1% (SE 6.3), respectively. Arbitrary cut-off PCI limits with 5-point splits ($p = 0.63$) were not predictive of a detrimental effect on survival as long as a complete CRS was achieved. A linear effect of the PCI on survival ($p = 0.62$) was not observed, and single-point PCI cohort splits within a PCI range of < 5 to > 10 were not predictive of survival for complete CRS patients. The PCI correlated with the ability to achieve a complete CRS, with a mean PCI of 14.7 (8.7) for completeness of cytoreduction (CC)0, 22.3 (7.8) for CC1 and 26.1 (9.5) for CC2/3 resections ($p = 0.0001$, hazard ratio 1.12, 95% confidence interval 1.09), with an

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HR of 1.15 for each 1-unit increase in the PCI score. Only 21% of the cohort achieved a complete CRS with a PCI ≤ 21 .

Conclusions—The PCI correlates with the ability to achieve a complete CRS in carcinomatosis from HGA. PCI is not associated with survival as long as a complete CRS can be achieved.

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is utilized in the treatment of peritoneal dissemination from a variety of epithelial primaries. The extent of disease at the time of CRS, as measured by the Peritoneal Carcinomatosis Index (PCI), has been shown to predict survival. It has been suggested that above a PCI limit that is variable depending on the type of primary tumor, even a complete CRS, is not associated with a survival benefit.^{1–3}

This concept is based on three dominant theories. The first, or ‘colony’, theory accepts that each metastatic site has its own metastatic potential. Therefore, a high volume of disease increases, in a logarithmic fashion, the chances of having a recurrence outside the peritoneal cavity, and offsets any potential locoregional benefits derived from CRS/HIPEC. The second, or mechanistic, theory suggests that in high-PCI states, micro-residual tumor is overseen and is left unaddressed during CRS. Lastly, the clonality theory points to the fact that after mitosis of a genetically altered cell, the resulting cells may be morphologically similar under hematoxylin and eosin light microscopy, but in reality they have distinct sequencing differences. Therefore, a high volume of disease incorporates genetic drifting, leading to multiple co-existing tumors with potentially different biologic behaviors.

The aim of the current work was to identify whether there was a PCI limit above which even a complete CRS/HIPEC is not associated with survival benefit for high-grade appendiceal (HGA) primaries.

METHODS

This was a three-institution, Institutional Review Board-approved, retrospective analysis of 622 CRS/HIPEC procedures performed for HGA adenocarcinoma between 1993 and 2015. Centers contributing data for the analysis were Basingstoke Hospital (England), University of Pittsburgh Medical Center (US), and Wake Forest University (US). Patients with incomplete or uncertain pathology data were excluded.

Data reviewed included demographics, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status,⁴ completeness of CRS, grade, signet ring subtype, nodal status, use of preoperative or postoperative chemotherapy, volume of peritoneal disease, and survival. HIPEC was administered using the closed abdominal technique. High grade was defined following the Bradley classification and included moderately or poorly differentiated adenocarcinoma, and signet ring cell primaries.⁵ CC0, R0, and R1 (microscopic disease) resections were grouped together as complete cytoreductions. CC1 (residual disease < 0.25 cm), CC2, and R2 cytoreductions (residual macroscopic disease) were characterized as incomplete cytoreductions.

Statistical Analyses

Descriptive statistics, included frequencies and proportions for categorical data, and means and standard deviations or medians and ranges for continuous data. Overall survival was calculated from the time of the CRS/HIPEC to the date of last follow-up or death. Survival estimates were calculated using the Kaplan–Meier method and the log-rank test was used to assess differences in survival between groups. Multivariate survival analysis was performed utilizing Cox proportional hazards regression. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). A p value ≤ 0.05 was considered to be statistically significant.

RESULTS

Between 1993 and 2015, 622 CRS/HIPEC procedures were performed in three tertiary peritoneal malignancy centers to address peritoneal dissemination of HGA primaries. A total of 101/622 (16%) cases were excluded due to incomplete data or uncertain pathology. Complete CRS was achieved in 260/521 patients (50%). HIPEC chemotherapy in the majority of patients (495/521, 95%), was mitomycin C, with a smaller group (23/521, 4.4%) treated with oxaliplatin.

Mean age for the entire cohort was 54.2 years (standard deviation [SD] 11.5, range 18–81), while mean PCI was 18.9 (SD 9.6, range 0–39). Nodal involvement was present in 32.1% of cases (111/346). Moderately differentiated primaries comprised 54/521 (10.4%), while signet ring cell carcinomas accounted for 51/521 (9.8%). The remaining cases were HGA adenocarcinomas (416/521, 79.9%). Neoadjuvant chemotherapy was delivered in 45.8% of cases (199/435) (Table 1).

Survival

The median survival for patients who achieved a complete CC0, R0, or R1 macroscopic CRS was 6.1 years, with 5- and 10-year survival rates of 51.7% (standard error [SE] 4.6) and 36.1% (SE 6.3), respectively. The median survival for the CC1 group was 1.8 years, with a 5-year survival rate of 23.0% (SE 4.1), while the median survival for CC2 and R2 resection was 1.6 years, with a 5-year survival rate of 15.6% (SE 4.3) (Fig. 1).

Survival Based on Variable Arbitrary Peritoneal Carcinomatosis Index (PCI) Cut-Off Limits

5-Point PCI Splits—Arbitrary cut-off PCI limits with 5-point splits ($p = 0.97$) were not predictive of a detrimental effect on survival as long as a complete CRS could be achieved (Table 2).

Single-Point PCI Splits (range 1–9)—Single-point PCI splits (range 1–10), compared with PCI ≥ 10 , were not predictive of survival ($p = 0.73$). The same was true when low-PCI patients were grouped as < 5 , 5–9, and $10 +$ ($p = 0.69$)

Single-Point Dichotomizing PCI Splits (range < 11 to < 31)—Dichotomizing the complete CRS cohort did not identify a PCI limit that was associated with prohibitive survival upon complete CRS (Table 3).

PCI Linear Effect

A linear effect of PCI on survival ($p = 0.94$) was not observed in those subjects with complete CRS. To assess the significance of the linear effect, a proportional hazards (Cox) regression model was used, with an estimated hazard ratio of 1.001 (per 1-unit increase) and a 95% confidence interval of 0.97–1.03.

PCI and the Ability to Achieve Complete Cytoreductive Surgery

PCI correlated with the ability to achieve a complete CRS ($p = 0.0001$, HR 1.12, 95% CI 1.09). More specifically, the mean PCI observed for CC0 resections was 14.7 (SE 8.7), and 22.3 (SE 7.8) and 26.1 (SE 9.5) for CC1 and CC2/3, respectively. PCI exhibited a linear significance, with the ability to achieve a complete macroscopic CRS (HR 1.035, 95% CI 1.02–1.05, $p < 0.0001$) for each 1-unit increase in PCI score. Consequently, only 31% (50/163) of patients achieved a complete CRS with a PCI ≥ 21 .

DISCUSSION

The extent of peritoneal disease at the time of CRS/HIPEC has been found to correlate with survival in patients with colon cancer. Various PCI thresholds ranging from 10 to 20 have been reported, whereby outcomes after CRS/HIPEC may not be beneficial to patients with peritoneal metastases.^{6–9} Most recently, it has been proposed that in patients with a PCI score > 17 , even a complete CRS does not offer a survival benefit; these patients have similar survival compared with patients receiving best supportive care with palliative intent.^{10–12} It is currently unknown if a PCI threshold exists for HGA primaries. To answer this question, we combined the operative experience of three major peritoneal malignancy centers and focused on the population who had a complete macroscopic CRS.

The presented analysis started with 5-point PCI splits, to factor in at least a 2-point variability of PCI calculation based on preoperative, intraoperative, or postoperative timing of recording.¹³ Five-point PCI grouping of the complete CRS cohort did not identify a PCI range above which post-treatment CRS/HIPEC survival was not meaningful. More specifically, median survival remained equal or higher to 4.5 years for all groups. Subsequently, single-point low-PCI splits (< 10) against the remaining cohort ($p = 0.73$) or in single-point dichotomizing splits, did not identify a PCI limit with detrimental effects on survival as long as a complete CRS was achieved. In the same fashion, a linear relationship between PCI and survival was not identified ($p = 0.94$), which is in contrast with what has been previously described for other primaries.^{11,14}

The significance of PCI lies in correlating with the ability to achieve a complete CRS ($p = 0.0001$). The relationship between the PCI and completion of CRS unfolds in a linear fashion per unit of PCI increase (HR 1.035, $p < 0.0001$). As previously demonstrated in other primaries, the completion of CRS in HGA primaries is directly predictive of overall survival;⁶ therefore, PCI indirectly predicts survival through the ability to achieve a CC0 resection, but not directly through a PCI threshold, as previously reported in colon cancer.¹¹ This may be explained by differences in biologic behavior, as indicated by differences in the gene expression profiles between colon and HGA primaries.¹⁵ It is important to point out

that the herein presented outcomes establish the validity of CC1 resections as incomplete CRS in HGA primaries. This is justified by the similar survival exhibited by CC1 and CC2/3 resections.

We believe that all three theories mentioned in the introduction (colony theory, residual disease and clonality) apply in HGA primaries but are heavily influenced by selection bias and tumor biology. The presented outcomes are generated from centers that have accumulated operating experience from thousands of cases, which, as previously shown, is pivotal in obtaining complete CRS in high-PCI patients.¹ It is also possible that the same institutional experience has influenced the exclusion of a subpopulation of patients with aggressive biologic behavior who would have later presented with dissemination outside the peritoneal cavity.

In addition, even though some degree of clonality is usually present in different primaries, not all clonality is equal. For example, clonality present in a low-grade appendiceal primary does not likely carry the same virulence as clonality present in colon cancer or HGA primaries.

This article has the limitations of a retrospective, multi-institutional analysis, including selection bias, institutional learning curves, unknown timing of PCI recording, and sequencing heterogeneity of what is currently accepted as HGA primaries. It is quite possible that subgroup analysis of signet ring primaries and primaries with lymphovascular invasion or positive lymph nodes, where aggressive tumor clonality is expected to be present, could have rendered a PCI range that directly predicts survival. The current cohort was underpowered to make such a distinction; therefore, even though this data set represents the largest HGA cohort currently available, institutional experience and proper patient selection should guide surgical decisions.

CONCLUSION

In HGA primaries, PCI correlates with the ability to achieve a complete CRS. Only one-third of patients had a complete CRS when the PCI was ≥ 21 . The PCI is not directly associated with survival as long as a complete CC0 macroscopic CRS can be achieved.

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FIG. 1.
Survival based on CC status of cytoreductive surgery ($p < 0.0001$). CC completeness of cytoreduction

TABLE 1

Demographic and baseline characteristics of the high-grade appendiceal group

	High-grade appendiceal tumors
Age, years [mean (SD)]	54.2 (11.5)
White	357/382 (93.5)
Black	16/382 (4.2)
Hispanic	2/382 (0.5)
Other	7/382 (1.8)
Male	256/519 (49.3)
Moderately differentiated	54/521 (10.4)
Poorly differentiated	416/521 (79.9)
Signet ring cell tumors	51/521 (9.8)
Neoadjuvant chemotherapy	199/435 (45.8)
PCI (mean)	18.9 (9.6)
Perfused with MMC	495/521 (95)
Perfused with oxaliplatin	23/521 (4.4)
ECOG	
0	137 (51.1)
1	92 (34.3)
2	32 (11.9)
3	7 (2.6)
CC0/R0/R1	260 (50.1)
CC1/CC2/R2	259 (49.9)
Positive nodes	111/346 (32.1)

Data are expressed as $n/N(\%)$ or $n(\%)$ unless otherwise stated*PCI* peritoneal cancer index, *MMC* mitomycin C, *ECOG* eastern cooperative oncology group, *CC* completeness of cytoreduction, *R* resection status

TABLE 2

PCI 5-point splits ($p = 0.97$) were not predictive of a detrimental effect on survival as long as complete cytoreductive surgery could be achieved

PCI	N	Median (years)
< 5	17	5.7+
5–9	45	4.5+
10–14	45	4.9
15–19	32	4.7
20–25	26	4.6
25 +	33	4.6

PCI peritoneal cancer index

TABLE 3

PCI single-point dichotomizing splits (range < 11 to < 31, $p = 0.97$) and survival

Split	p-value	HR	95% CI	Split	p-value	HR	95% CI
< 11	0.78	0.92	0.52–1.64	< 22	0.88	0.95	0.50–1.81
< 12	0.59	0.86	0.49–1.50	< 23	0.90	0.96	0.49–1.86
< 13	0.41	0.80	0.46–1.38	< 24	0.87	0.94	0.48–1.88
< 14	0.83	1.06	0.62–1.81	< 25	0.79	0.91	0.46–1.81
< 15	0.92	0.97	0.57–1.66	< 26	0.96	1.02	0.48–2.16
< 16	0.83	1.06	0.62–1.84	< 27	0.70	1.18	0.51–2.77
< 17	0.88	1.04	0.60–1.82	< 28	0.78	1.12	0.48–2.63
< 18	0.79	0.93	0.53–1.62	< 29	0.20	2.49	0.61–10.25
< 19	0.82	0.94	0.53–1.65	< 30	0.30	2.11	0.51–8.69
< 20	0.78	0.92	(0.52, 1.62)	< 31	0.78	1.22	0.30–5.02
< 21	0.69	0.89	(0.49, 1.61)				

PCI peritoneal cancer index, HR hazard ratio, CI confidence interval