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Correlation Between Intraoperative and Pathological Findings for Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background. This study aimed to examine the correlation between intraoperative and pathological findings for patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) and to determine their prognostic significance.

Methods. Pathological reports of all colorectal cancer (CRC) patients undergoing CRS/HIPEC between 2009 and 2016 were retrospectively reviewed. Pathological specimens lacking tumor cells were defined as negative pathological specimens (NPS). The intraoperative peritoneal cancer index (PCI) and pathological PCI (excluding NPS) were calculated separately. Receiver operating characteristic (ROC) curves were applied to compare the prognostic value of intraoperative and pathological scoring systems.

Results. For 108 CRC patients, 113 CRS/HIPEC procedures were performed. Of 959 pathological specimens examined, 178 (18.6%) were NPS. Overall, 78 procedures (69%) showed NPS. In 52 procedures (46%), the pathological PCI differed from the intraoperative PCI ($\Delta PCI > 0$). The ROC areas for intraoperative PCI and pathological PCI were similar in predicting 1-year overall survival (OS), 2-year OS, and 1-year disease-free survival (all p values not significant). However, for the patients with NPS, the number of positive specimens (containing tumor tissue) was superior to intraoperative PCI in predicting 2-year OS (ROC under the curve areas, 0.69 vs. 0.58, respectively; $p = 0.012$). In addition, a subgroup of 15 patients with a high ΔPCI (≥ 3) had a more favorable median OS than a matched group of 30 patients with similar intraoperative PCI and a ΔPCI of 0 (median survival not reached vs. 21.6 months, respectively; $p = 0.05$).

Conclusions. In the majority of CRC CRS/HIPEC procedures, NPS may be found. Among patients with NPS, pathological correlation may have a prognostic significance.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is an aggressive but effective treatment for selected patients with peritoneal metastasis (PM) of colorectal (CRC) origin. The efficacy of CRS/HIPEC in CRC PM has been demonstrated in multiple retrospective studies[1–5] and in one prospective randomized controlled trial, in which CRS/HIPEC was associated with longer survival than systemic chemotherapy alone.[6]

The peritoneal cancer index (PCI), assessed by the surgeon intraoperatively, is a well-established prognostic predictor for patients undergoing CRS/HIPEC.[6–8] However, lesions considered clinically malignant and consequently resected may not contain viable tumor tissue in the histopathologic examination. In fact, several studies have shown that in some CRS/HIPEC procedures, no residual viable tumor tissues were found in any of the resected specimens.[9,10]

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Because the prognostic value of pathological tumor burden remains unclear, we hypothesized that pathological tumor burden may reflect the true extent of PM and correlate better with oncologic outcomes than intraoperative PCI. Therefore, our study aimed to examine the correlation between intraoperative and pathological findings for patients undergoing CRS/HIPEC at a single tertiary referral institution and to determine whether this correlation has prognostic significance.

METHODS

Study Design

Data were obtained from a single-center prospectively collected database after approval was received from the Independent Ethical Committee. Pathological reports of all CRC patients undergoing CRS/HIPEC at our institution between 2009 and 2016 were reviewed. Pathological and intraoperative tumor burden were calculated separately and correlated with oncologic outcomes as described later.

Because our study aimed to correlate pathological tumor burden and prognosis, only patients who underwent complete CRS/HIPEC were included in the analysis.

Operative Technique

Surgery began routinely with a midline laparotomy, enterolysis if required, and exploration of the abdominopelvic cavity. The PCI was recorded according to the Sugarbaker classification.[11] The abdominopelvic cavity was divided into 13 regions, and each region received a score of 0–3 PCI points according to the size of its largest lesion. The individual scores of these regions then were summed to establish a total PCI score of 0–39.

Next, cytoreduction was performed, including resection of the primary tumor (if not previously resected), omentectomy, resection of involved intraabdominal organs, and stripping of involved parietal peritoneum surfaces according to the peritonectomy procedures described by Sugarbaker[12].

After cytoreduction, the completeness of cytoreduction (CC) score was recorded according to the Sugarbaker classification.[11] Complete cytoreduction was defined as a CC score of 1 or lower. Then HIPEC was delivered using mitomycin C as the most common chemotherapeutic agent (98%). From July 2009 to January 2014, HIPEC was delivered by the open "coliseum" technique. Beginning February 2014, HIPEC was delivered by the closed abdomen technique. After the administration of HIPEC, gastrointestinal anastomoses were created.

Quantification of Pathological Tumor Burden

Surgical specimens from patients who underwent complete CRS/HIPEC were sent to the pathology department and routinely fixed in 4% buffered, pH 7.2–7.4 formaldehyde. Representative tissue portions were embedded in paraffin, sliced into 3- to 4-μm-thin sections, and stained with hematoxylin and eosin. Pathology reports of all the patients were reviewed and compared with operative reports to determine whether resected lesions considered malignant during the surgery actually consisted of tumor cells. A pathological specimen lacking tumor cells was defined as a negative pathological specimen (NPS).

Only a specimen labeled as malignant intraoperatively was defined as an NPS, whereas a frozen-section biopsy and an organ resected prophylactically, such as the omentum, was not considered an NPS. The pathological PCI was calculated using the same method, as previously described, after NPS were excluded from the calculation. Delta PCI was defined as the difference between intraoperative PCI and pathological PCI. In addition to pathological PCI, two other scales of pathological tumor burden were recorded from pathology reports for each patient: the total number of specimens resected (excluding prophylactic resections) and the number of positive specimens resected (number of NPS subtracted from the total number of specimens resected).

Patient Follow-up Evaluation

After CRS/HIPEC, the patients were followed every 3 months by history and physical examination. Contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis, or positron emission tomography (PET)-CT scan (in cases showing preoperative fluorodeoxyglucose avidity) were performed routinely every 6 months during the first 2 years, and then every 12 months or according to clinical judgment afterward. Serum carcinoembryonic antigen (CEA) level as well as CA-19-9 and CA-125 levels were examined every 6 months. Disease recurrence was defined as any appearance of a new intraabdominal or extraabdominal lesion documented by cross-sectional imaging or any increase in levels of serum markers in two consecutive tests after CRS/HIPEC.

Statistical Analysis

Data were analyzed with SPSS version 22 (SPSS, Chicago, IL, USA). Categorical variables, expressed as percentages, were compared by the Chi square test or Fisher's exact test. Continuous variables, expressed as mean ± standard deviation or median (range), were

compared by Student's *t* test and the Mann–Whitney/Kruskal–Wallis test, respectively. Receiver operating characteristic (ROC) curves were applied to compare the prognostic value of intraoperative PCI with pathological estimates of tumor burden. The correlation between the total number of specimens resected and intraoperative PCI was examined using Pearson's correlation. Overall survival (OS) probabilities, measured from the date of CRS/HIPEC, were calculated using the Kaplan–Meier method, and subgroups were compared with the log-rank test. To determine whether high delta PCI has an impact on survival, all patients with a delta PCI of 3 or higher were matched (1:2 ratio) to patients with a delta PCI of 0 according to intraoperative PCI. Survival differences between the groups then were compared using the Kaplan–Meier method. A p value lower than 0.05 was defined as significant.

RESULTS

From 2009 to 2016, 135 CRC patients with PM underwent explorative laparotomy with curative intent. After exclusion of 19 patients who underwent aborted procedures (received no HIPEC) and 8 patients who underwent incomplete cytoreduction with HIPEC, 108 patients who underwent 113 CRS/HIPEC procedures constituted the study population. Of 959 pathological specimens examined (median, 8 per patient; range 1–22), 470 specimens (49%) were positive by histopathologic examination (i.e. specimens labeled as malignant intraoperatively and found to have viable tumor tissue in the histopathologic examination), 247 specimens (26%) were prophylactic resections (i.e. specimens not labeled as malignant intraoperatively but resected prophylactically), and 178 specimens (18.6%) were NPS (Fig. 1). Lesions resected from the bowel serosa/mesentery were the most common type of NPS (34%). Other types of NPS included parietal peritoneum, small bowel, abdominal wall, and other resections (Fig. 1).

Overall, NPS were found in 78 CRS/HIPEC procedures (69%), and in 52 procedures (46%), pathological PCI differed from intraoperative PCI (median delta PCI, 2 points; range 1–10 points). The median number of NPS was 1.5 (range 1–13). In five patients, all examined specimens were NPS. The univariate analysis of factors associated with NPS is presented in Table 1. None of the preoperative factors examined was associated with the presence of NPS, whereas the intraoperative PCI score and the number of resected specimens were the only significant intraoperative factors.

The proportion of patients with NPS has increased over time, with NPS found in 57.9% of the first 38 consecutive CRS/HIPEC cases (April 2009 to August 2012), 65.8% of the next 38 cases (September 2012 to January 2015), and 83.8% of the last 37 cases (February 2015 to February 2016) ($p = 0.046$). The corresponding median numbers of NPS per procedure [1 (range 0–3), 1 (range 0–7), and 2 (range 0–13); $p = 0.001$] and the median intraoperative PCI scores [5 (range 2–19), 5 (range 2–29), and 10 (range 2–25); $p < 0.001$] during these periods also have increased significantly.

All the CRS/HIPEC procedures were performed by two surgical teams from different departments. The proportion of patients with NPS was significantly higher for one of the teams [28 of 31 procedures (90.3%) vs. 50 of 82 procedures (61.0%); $p = 0.003$]. The corresponding median number of NPS per procedure [2 (range 0–7) vs. 1 (range 0–13); $p < 0.001$] and median intraoperative PCI score [11 (range 3–29) vs. 5 (range 2–20); $p < 0.001$] also differed significantly between the surgical teams.

The median follow-up period was 26.5 months, during which 67 patients (62%) died. The median OS was 34.5 months, and the median disease-free survival was 9.7 months. We found a statistically significant correlation between the total number of specimens sent to pathology during CRS/HIPEC (excluding prophylactic resections) and OS (Fig. 2). The median OS was 54 months for 1–3

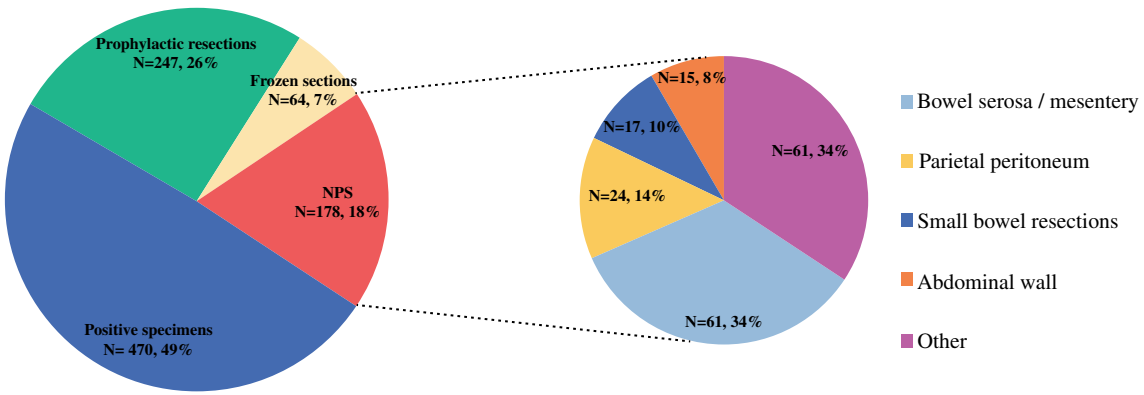

FIG. 1 Distribution of overall pathological specimens and negative pathological specimens (NPS)

TABLE 1 Univariate analysis of pre- and intraoperative factors associated with the presence of negative pathological specimens (NPS)

	CRS/HIPEC procedures with NPS (n = 78)	CRS/HIPEC procedures without NPS (n = 35)	p value
Mean age (years)	57.5 ± 13.7	61.7 ± 9.8	0.08
Gender: n (% males)	33 (42.3)	10 (28.6)	0.16
Location of primary tumor: n (% right sided)	44 (56.4)	20 (57.1)	0.94
Nodal status at presentation: n (% N stage > 0)[a]	50 (69.4)	21 (65.6)	0.70
Tumor stage at presentation: n (% T4 stage)[a]	22 (30.1)	9 (28.1)	0.83
Previous abdominal surgery: n (% patients)	75 (96.2)	33 (94.3)	0.65
Mean time from original surgery to CRS/HIPEC (years)	2.0 ± 1.6	2.4 ± 1.6	0.19
Chemotherapy given before CRS/HIPEC: n (% patients)	72 (92.3)	31 (88.6)	0.52
Intraoperative PCI score: median (range)	8 (2–29)	4 (2–25)	0.002
Mean surgery duration (h)	6.5 ± 2.4	6.8 ± 2.3	0.46
Frozen-section biopsies taken: n (% patients)	28 (35.9)	12 (34.3)	0.87
No. of specimens resected: median (range)	8 (2–21)	5 (1–22)	< 0.001

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal cancer index

[a]Missing staging data in 8 cases

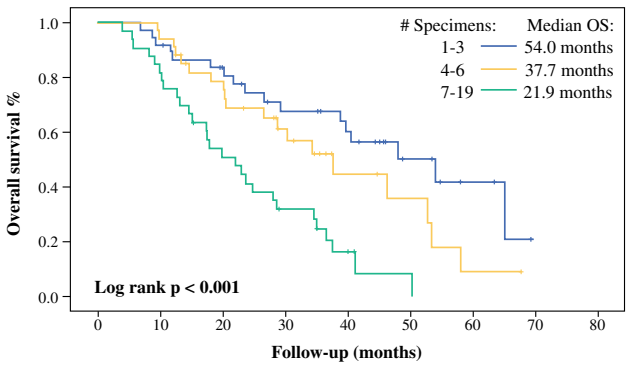

FIG. 2 Correlation between the number of specimens sent to pathology during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) and overall survival (OS)

specimens, 37.7 months for 4–6 specimens, and 21.9 months for 7–19 specimens ($p < 0.001$). The number of specimens sent to pathology also showed a linear correlation with intraoperative PCI (Pearson's $r = 0.82$; $p < 0.001$).

The ROC under the curve areas for intraoperative PCI and pathological PCI were similar in predicting 1-year OS (0.60 and 0.61, respectively; $p = 0.88$), 2-year OS (0.65 and 0.68, respectively; $p = 0.75$), and 1-year disease-free survival (0.78 and 0.80, respectively; $p = 0.68$), as depicted in Fig. 3. However, when this analysis was restricted to patients with NPS ($n = 78$), the number of positive specimens was superior to intraoperative PCI in predicting 2-year OS (ROC under the curve areas, 0.69 vs. 0.58, respectively; $p = 0.012$; Fig. 3D). In addition, a subgroup of 15 patients with high delta PCI (≥ 3) had a more favorable median OS than a matched group of patients with similar intraoperative PCI and a delta PCI of 0 (median survival, not reached vs. 21.6 months, respectively; $p = 0.05$; Fig. 4).

DISCUSSION

Currently, CRS/HIPEC is gaining acceptance as an effective treatment method for selected patients with PM of CRC origin. The natural history of patients with CRC PM referred to palliative care is associated with a poor median survival of 5–12 months.[13] Systemic therapy combining cytotoxic and biologic agents may improve the median survival, up to 19 months,[14] and CRS/HIPEC, may significantly improve median and overall survival for selected CRC PM patients, with a median survival reaching 30–60 months.[15]

The most important prognostic determinants for patients undergoing CRS/HIPEC are the volume of peritoneal disease, as reflected by the PCI score, and the completion of cytoreduction.[2,7] The PCI score, a quantitative factor calculated by the surgeon intraoperatively, may not represent the presence of viable tumor tissue. To the best of our knowledge, our study was the first to correlate intraoperative and pathological PCI.

Surprisingly, we found that in about two thirds of CRS/HIPEC procedures, some lesions resected during the surgery and considered malignant by the surgical team did not eventually contain viable tumor tissue in the final histopathologic examination. Furthermore, in about half of the CRS/HIPEC procedures, the intraoperative PCI was higher than the pathological PCI.

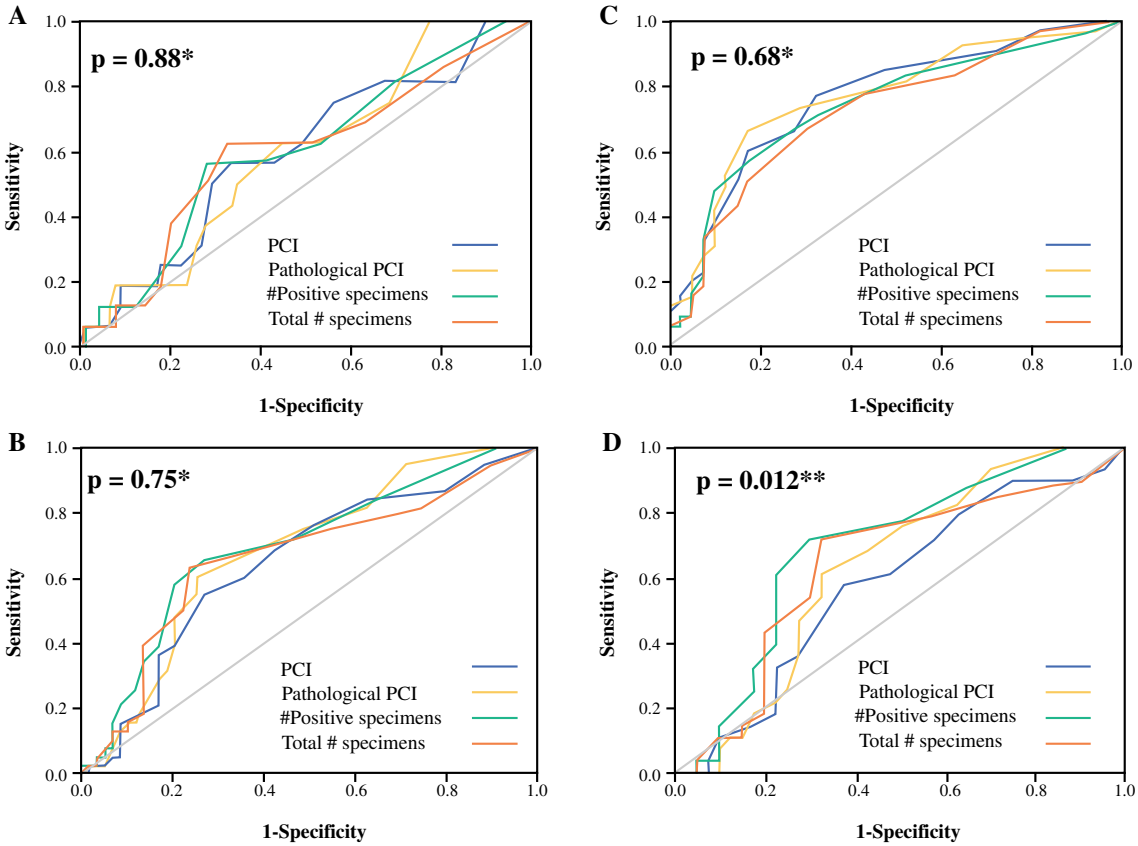

FIG. 3 Receiver operating characteristic curves for intraoperative peritoneal cancer index (PCI) and various pathological scales of tumor burden in predicting, **a** 1-year overall survival, **b** 2-year overall survival, **c** 1-year disease-free survival, and **d** 2-year overall survival restricted to patients with negative pathological specimens (n = 78). *p value refers to PCI versus pathological PCI. **p value refers to PCI versus number of positive specimens

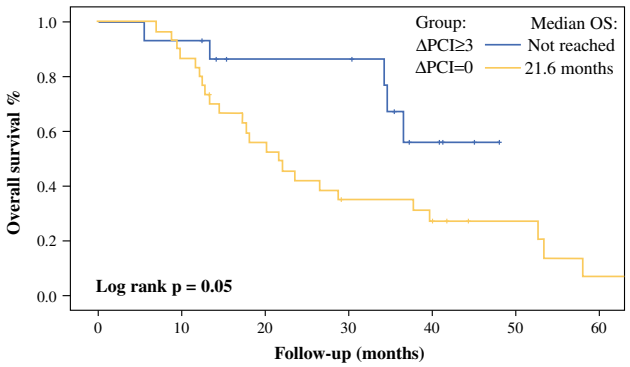

FIG. 4 Overall survival (OS) analysis of 15 patients with a delta peritoneal cancer index (PCI) of 3 or higher and a matched group (1:2 ratio) of 30 patients with similar intraoperative PCI and a delta PCI of 0. The median intraoperative PCI in both groups was 8 (range 3–19)

Several explanations can be given for the presence of NPS. One proposed mechanism is the response of cancerous lesions to preoperative systemic chemotherapy. Passot et al.[10] demonstrated that about 10% of CRS/HIPEC procedures performed for CRC patients after systemic chemotherapy resulted in a pathological complete response (defined as the absence of residual cancer cells in all specimens), which was associated with a better prognosis. In this regard, it should be emphasized that not all patients in our cohort received preoperative chemotherapy, so this mechanism cannot exclusively account for NPS. In addition, the fact that the proportion of patients who received preoperative chemotherapy did not differ significantly between the patients with NPS and those without NPS (Table 1) also implies another cause.

A second explanation for the presence of NPS, proposed by Enblad et al.[9], is overestimation of intraoperative PCI due to misjudgment of scarring and fibrosis as tumor. Because most CRS/HIPEC procedures are performed metachronously after a previous colorectal resection, and because only a minority of cases consist of a synchronous colorectal resection together with cytoreduction, the subsequent formation of intraabdominal scar tissue that resembles tumor lesions is logical. Nevertheless, the incidence of previous abdominal surgery among patients without NPS was similarly high (Table 1), raising questions about causality between previous surgery and NPS. In

this regard, it should be emphasized that data regarding the extent of primary surgery were not available for statistical analysis.

A third proposed explanation for the presence of NPS in patients undergoing CRS/HIPEC is the use of this procedure for prophylactic purposes. Although prophylactic HIPEC is gaining popularity for patients with CRC and appendiceal malignancies,[16–18] our group of patients did not include cases treated prophylactically, and organs resected prophylactically were not considered as NPS.

A fourth proposed explanation for the presence of NPS in patients undergoing CRS/HIPEC is sampling error. Due to the large number of specimens and their volume, histopathology sampling covers about 1% of the submitted tissues. Extensive sampling may increase the workload of the pathologist and as a result may delay the pathology report. Enhanced pathological examination may yield additional lesions, as shown in lymph node sampling in colon cancer.[19] However, it is of little value and will delay the pathological report.

The only significant factors found to predict NPS in a univariate analysis were intraoperative PCI score and number of specimens resected. This finding suggests that in cases with a heavier intraabdominal tumor burden (as estimated by the surgeon intraoperatively), resulting in resection of more lesions, the chances of finding NPS are higher. This supports the under-sampling theory. In this regard, we also assume that differences in intraoperative PCI values resulting from trends in patient selection may account for the observed changes in NPS proportion over time and the disparity between surgical teams. The fact that NPS rates have increased over time suggests that no relation exists between NPS and surgical inexperience or the CRS/HIPEC institutional learning curve.

Interestingly, frozen-section biopsies did not play a role in reducing the prevalence of NPS, as presented in Table 1. We advocate the use of frozen-section biopsies only in cases requiring intraoperative decisions whether to resect a critical lesion such as a lesion involving the ureter, major blood vessels, or hepatobiliary structures. In these cases, a negative frozen-section biopsy may facilitate surgery and prevent unnecessary organ resection, which may cause significant postoperative morbidity. Given that most types of NPS have required only relatively minor operative procedures, including resection of bowel serosa, peritoneal surfaces, or abdominal wall (Fig. 1), it is prudent to assume that frozen-section biopsies were not required in these cases. This may explain the fact that frozen-section biopsies were not associated with lower rates of NPS.

Pathological correlation of PCI may have implications for determination of operability and prognosis. With regard to operability, the limit on the extensiveness of CRC PM amenable to effective CRS/HIPEC treatment is placed at a PCI of about 17–20. A higher PCI score has been shown to correlate with poor oncologic outcome and higher perioperative morbidity.[8,20,21] Theoretically, pathological correlation may change inoperable patients to operable patients by lowering the actual PCI score. However, this is unlikely because delta PCI was modest in most cases. In addition, intraoperative assessment of pathological tumor burden is impractical. It should be noted that our cohort did not include CRS/HIPEC cases aborted due to high PCI, so assessment of pathological PCI as a means to increase operability was beyond the scope of this study.

Regarding prognosis, ROC analysis showed that pathological PCI could not predict oncologic outcomes better than intraoperative PCI. Again, this could have been attributable to the fact that the difference between intraoperative and pathological PCI was negligible in most cases. However, analysis restricted to patients with NPS showed that the number of positive specimens was superior to intraoperative PCI in predicting 2-year OS (Fig. 3d). In addition, a subgroup of patients with high delta PCI had more favorable OS than a matched subgroup with a delta PCI of 0 (Fig. 4). These findings suggest that pathological estimates of tumor burden may predict prognosis better than intraoperative PCI in selected NPS cases. In such circumstances, pathological estimates may serve as an important prognostic tool for predicting individual patient outcome and administration of post-CRS/HIPEC adjuvant systemic therapy.

Our study was limited by its small sample and its retrospective nature. In addition, this study included only patient chart review, and actual revision of pathological specimens was not performed by a pathologist. Therefore, some specimens classified as NPS may represent a false-negative error. Furthermore, subgroups in our matched pair analysis may have been unbalanced in terms of baseline characteristics other that PCI. Finally, some patients were lost to follow-up evaluation because our institution is a tertiary referral center.

In conclusion, the intraoperative PCI frequently overestimates the true burden of peritoneal disease. Our findings suggest that NPS may be found in a majority of CRC CRS/HIPEC procedures. Among patients with NPS, pathological correlation may have a prognostic significance.

DISCLOSURE There are no conflicts of interest.

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