Tumour Load in Advanced Ovarian Cancer Patients and Its Validation by Radiological Peritoneal Cancer Index (PCI) Score

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ABSTRACT

Objective: To compare the radiological peritoneal cancer index (PCI) score to the surgical PCI score for validating it as a non-invasive method to predict surgical outcomes.

Study Design: A descriptive study.

Place and Duration of the Study: Department of Obstetrics and Gynaecology of the Aga Khan University Hospital, Karachi, Pakistan from September 2021 to May 2022.

Methodology: All successive patients diagnosed with advanced-stage ovarian cancer were enrolled in the research. Prior to surgery, the severity of ovarian cancer was evaluated using the Sugarbaker Peritoneal Cancer Index score derived from radiological imaging. The score was compared to the surgical PCI score determined during the surgery. The correlation between the scores and residual tumour status was confirmed.

Results: The study included a total of 26 patients. The mean age of patients was 50.17 years, with a standard deviation of 11.04. Five (19.2%) patients underwent surgery first, whereas 21(80.8%) needed interval debulking surgery after receiving chemotherapy in the neoadjuvant setting. The interclass correlation value among radiological and surgical (PCI) was 0.52, with a 95% confidence interval ranging from 0.17 to 0.75. The Bland-Altman plot displays the agreement amongst the PCI scores, indicating a bias of 1.115 with a 95% confidence interval of 4.61. Surgical exploration revealed zero residual disease in 90% of persons with a PCI score <10. Patients with a PCI score <10 had significantly brief operative time and reduced blood loss compared to those with a score >10. Patients with a PCI score below 10 had also fewer complications.

Conclusion: PCI is an efficient means for anticipating the success of surgery and the existence of residual disease without invasive measures. This can be very helpful in deciding the best time for surgery.

Key Words: *Peritoneal cancer index, Advanced ovarian cancer, Carcinomatosis, Prognosis, Tumour load.*

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INTRODUCTION

Ovarian malignancies are considered one of the most devastating gynaecological cancers due to their impact on morbidity, recurrence, and survival rates. Their appearance in advanced stages is well-known, with a five-year survival of less than 45%.[1] Even with optimal cytoreductive surgery (CRS) and chemo-therapy in an adjuvant setting 70 - 80% of patients develop recurrence of disease within 5 years of primary treatment.[2] The best prognostic factor in patients with ovarian cancer (OC) is surgery with no residual disease. Complete removal of visible tumour is linked to improved overall and progression-free survival.[3,4]

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In 2018, the global incidence of new OC cases was about 300,000 with approximately 200,000 fatalities attributed to OC.[5] As per Pakistan's global health survey, the overall incidence of carcinoma of ovary is 2.4%. Globocan 2020 reported 4,326 new cases of OC with 2,946 deaths in Pakistan.

The mainstay of the treatment of OC is debulking surgery supported by adjuvant chemotherapy. However, in cases of advanced OC with massive ascites or pleural effusion, peritoneal or upper abdominal disease at presentation, neo-adjuvant chemotherapy (NACT) followed by debulking surgery is preferred. This approach not only aids in reduction of tumour bulk but also enables subsequent debulking surgery a success with lesser morbidity.[6-9]

As most OC patients are detected in advanced stage (Stage III/IV), it is prudent to identify cases that are not amenable to upfront CRS. Attempting CRS in these cases might lead to incomplete cytoreduction or even the open-close procedure with a failed attempt. Therefore, it is a challenge to correctly identify the extent of peritoneal carcinomatosis and disease-spread by noninvasive methods before embarking on surgical

attempt. In 1998, Jacquet and Sugarbaker created a Peritoneal Cancer Index (PCI) score to evaluate the spread of peritoneal illness in gastrointestinal cancers.[10] Quantifying this score aids in standardising the therapy options for each patient. CT-PCI is not included in the current recommendations for diagnosing and treating OC. However, several research studies have utilised this score to evaluate the severity of disease in OC and to determine resectability, resulting in positive outcomes.[11-13]

The objective of this study was to compare the radiological PCI score with the surgical PCI score in order to validate the use of this score as a noninvasive method for predicting surgical outcomes. It will greatly assist physicians in correctly assigning patients to the best treatment option, whether it is upfront CRS or chemotherapy in neoadjuvant settings.

METHODOLOGY

This was a single-centric cross-sectional study, carried out in the Obstetrics and Gynaecology Department of the Aga Khan University Hospital, from September 2021 to May 2022. Institutional Ethical approval was acquired prior to the study (ERC #: 2021-6476-18811).

All sequential patients diagnosed with advanced-stage OC who underwent upfront or interval debulking surgery during the study period were considered for inclusion. Patients with recurrent OC were excluded from the study.

A CT scan of the abdomen, chest, and pelvis was performed for all the patients. The radiological PCI was obtained and recorded by a designated radiologist pre-operatively. The surgical PCI score was estimated at the start of the procedure. There were 13 designated regions for the anatomic distribution. Nine areas comprised the abdominopelvic cavity, which is divided into two transverse planes and two sagittal planes. The small bowel was designated by regions 9-12. The largest diameter of the tumour implants dispersed throughout the peritoneal surfaces was referred to as the lesion size (LS), which ranged from 0 (no tumour visible) to 3 (tumour ≥5 cm). The PCI score ranges between 0 and 39.

The surgeon documented the state of residual tumour at the end of procedure. The surgical procedure aimed to achieve full cytoreduction by removing all the visible tumours. All surgeries were conducted by a trained Gynaecological Oncologist.

The residual disease was classified as R0, R1, and R2. It was labelled as R0 (complete cytoreduction) where zero residual disease was left behind at the completion of surgery. R1 (optimal cytoreduction) was labelled in cases where the residual disease was <1cm in diameter, and R2 (suboptimal cytoreduction) if the residual disease status was >1cm in diameter.[12] Postoperatively any complication within 30 days was graded by the Clavien-Dindo classification system.

Sample size was calculated by the assumption that agreement between surgical PCI and radiological PCI can be quantified using the differences between observations made on the same subjects. Assuming a mean and standard deviation of differences of 0.5 ± 1.5 between radiological and surgical PCI, a minimum of 26 patients with OC were enrolled to achieve 95% level of agreement and power of 80%. The maximum mean difference of 5 was allowed between the two methods.

The data were entered into SPSS or Excel and then transferred to statistical software such as STATA. Mean and standard deviation were calculated for all the quantitative variables in the dataset, such as age, BMI, pre-operative CA-125 level, etc. The normality of continuous data was evaluated by Kolmogorov-Smirnov or Shapiro-Wilk's test. Frequencies and percentages were calculated for all qualitative characteristics such as surgical strategy, type of surgery, and histological type. Chi-square test or Fisher's exact test was used for categorical data and Mann-Whitney U test was used for median comparison between complete and incomplete CRS.

Composite scores combining radiological and surgical PCI were utilised for further study. The Bland-Altman scatterplot approach was utilised to assess the agreement between radiological and surgical PCI by graphing the average PCI difference *versus* the average PCI score. A clinically acceptable cut-off PCI score was determined to differentiate between resectable and unresectable disease. This allowed for the computation of sensitivity, specificity, and negative and positive predictive value of the radiological PCI score. The Spearman's rank correlation coefficient was utilised to explore the relationships between the radiological and surgical PCI. A $p \leq 0.05$ was considered as significant.

RESULTS

A total of 26 women with OC underwent surgical cytoreduction during the study period and were recruited in the study. The average age of patients was 50.17 ± 11.04 years (range: 27-71) and 77% (20/26) of them were multiparous women. The demographic and tumour features of the patients are outlined in Table I. Most patients had Stage IIIC 14 (53.8%) and Stage IV 5 (19.2%) disease. Among 26 patients, 21 (80.8%) underwent neoadjuvant chemotherapy (NACT) before interval debulking surgery, while 5 (19.2%) had upfront CRS (Table I).

Table I: Demographics and tumour statistics.

Variables	Statistics
Age (years)	50.15 ± 11.04
BMI (kg/m^2)	27.35 ± 5.27
Parity	
Nullipara	6 (23.1%)
Multipara	20 (76.9%)
FIGO stage	
I	3 (11.5%)
IIA	4 (15.4%)
IIIC	14 (53.8%)
IV	5 (19.2%)
Neoadjuvant treatment	
Yes	21 (80.8%)
No	5 (19.2%)
Upfront surgery	
Upfront cytoreductive surgery	5 (19.2%)
Interval debulking surgery	21 (80.8%)
Total duration of surgery (min)*	180 [147.5 - 210]
Estimated blood loss (ml)*	450 [300 - 625]

**Median [25th-75th percentile].*

Table II: Comparison of characteristics with complete and incomplete CRS.

Variables	Complete CRS n = 22	Incomplete CRS n = 4	p-value
Age (years)*	50.5 [40 - 59]	50 [42.75 - 57.75]	0.972
BMI (kg/m^2) *	28 [23 - 30.25]	26 [22 - 33.75]	0.864
PCI surgical*	6 [3 - 9]	10.5 [6.25 - 23]	0.096
PCI radiological*	5 [2 - 7.5]	8.5 [2.7 - 13.5]	0.352
Parity			0.542
Nullipara	6 (27.3%)	0 (0%)	
Multipara	16 (72.7%)	4 (100%)	
FIGO stage			0.306
I	3 (13.6%)	0 (0%)	
IIA	4 (18.2%)	0 (0%)	
IIIC	12 (54.5%)	2 (50%)	
IV	3 (13.6%)	2 (50%)	
Neoadjuvant treatment			0.555
Yes	17 (77.3%)	4 (100%)	
No	5 (22.7%)	0(0%)	
Upfront surgery			0.555
Upfront cytoreductive surgery	5 (22.7%)	0 (0%)	
Interval debulking surgery	17 (77.3%)	4 (100%)	
Total length of surgery (min)*	180 [150 - 210]	150 [93.7 - 225]	0.371
Approximate blood loss (ml)*	450 [300 - 550]	425 [175 - 1125]	0.829
Complication during surgery	4 (18.2%)	1 (25%)	0.999

Data are presented as n (%) and median [25th - 75th percentile]. Statistics were obtained by Chi-square tests and Mann-Whitney U test.*

Table III: Diagnostic accuracy of surgical and radiological PCI >10 (n = 26).

Parameters	For Surgical PCI cut-off ≥10		For Radiological PCI cut-off ≥10	
	n/N	Estimates (95% CI)	n/N	Estimates (95% CI)
Sensitivity	2/4	50% (15 - 85)	2/5	40% (11.76 - 76.93)
Specificity	20/22	90.91% (72.18 - 97.47)	19/21	90.5% (71.09 - 97.35)
Positive predictive value	2/4	50% (15 - 85)	2/4	50% (15 - 85)
Negative predictive value	20/22	90.91% (72.81 - 97.47)	19/22	86.4% (66.66 - 95.25)
Diagnostic accuracy	22/26	84.62% (66.47 - 93.85)	21/26	80.77% (62.12 - 91.49)

For surgical PCI ≥10: True positives = 2, false positives = 2, false negatives = 2, true negatives = 20 For radiological PCI ≥10: True positives = 2, false positives = 2, false negatives = 3, true negatives =19. Sensitivity = (True Positives) / (True positives +False negatives). Specificity = (True negatives) / (True negatives +False positives). PPV = (True positives) / (True positives +False positives). NPV = (True negatives) / (True negatives +False negatives).

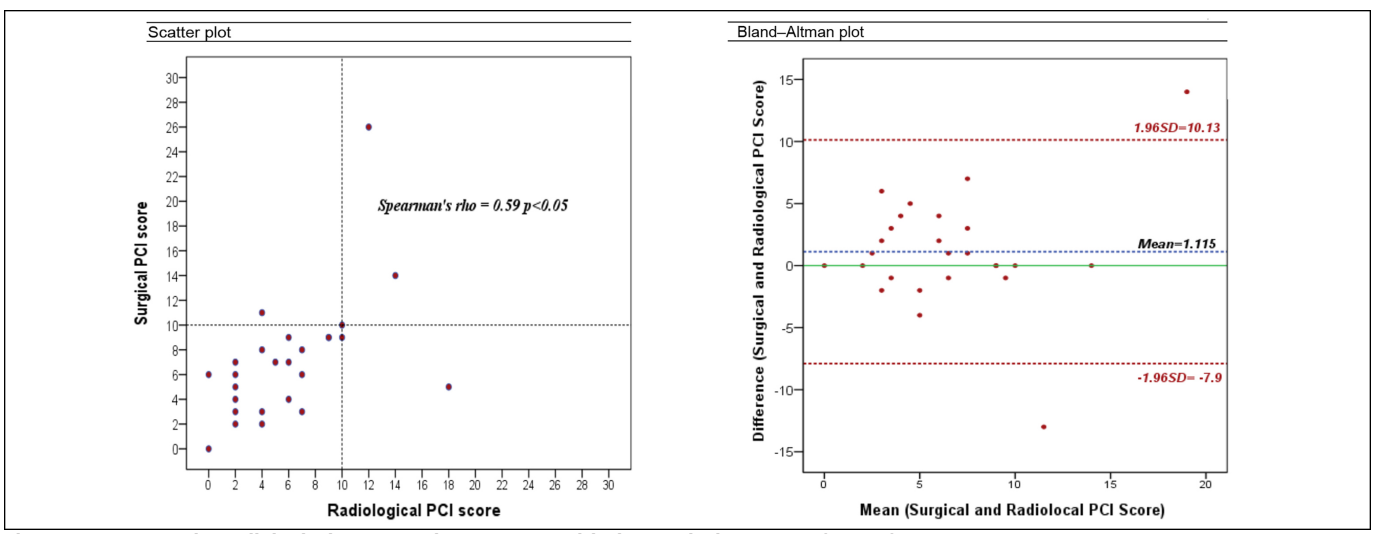

Figure 1: Compare the radiological preoperative PCI score with the surgical PCI score (n = 26).

Radiological and surgical median PCI scores were 5.50 (Range: 0 - 18 and IQR = 2 - 9) and 6.5 (range: 0 - 26 >IQR = 3.7 - 9), respectively. Twenty-two (84.62%) patients had complete CRS, while 4 (15.38%) patients had incomplete CRS. Three of the four cases with incomplete CRS had optimal CRS (<1cm residual), whereas one had suboptimal CRS (>1cm residual). Patients with an incomplete CRS had a higher median PCI score as compared to those with a complete CRS but no statistically significant difference was observed (radiological: 10.5 *vs.* 6; p = 0.096 and surgical: 8.5 *vs.* 5 p = 0.352). Similarly, demographic and tumour characteristics were also not statistically significant in patients with complete and incomplete CRS (Table II).

Bias and 95% limits of agreements between the radiological and surgical PCI score are shown in the Bland-Altman plot (Figure 1). The mean difference (bias) of the measurements of PCI score between surgical and radiological methods was 1.115 ± 4.607. A favourable bias, favouring the surgical PCI score by 1.12 units compared to the radiological PCI score was seen, however, it was not statistically significant ($p = 0.229$). The 95% limits of agreement (-7.9, 10.13) contained 92% (24/26) of the difference scores, indicating moderate agreement. Similarly, the Spearman's correlation between the score was $r_p = 0.59$ [95% CI: 0.26 - 0.80; $p < 0.05$] and the intraclass correlation was ICC = 0.517 (95% CI: 0.17 - 0.75; $p < 0.01$). The upper bond of the CI has demonstrated the moderate reliability of radiological and surgical PCI scores.

The sensitivity and specificity of radiological PCI in the detection of residuals (PCI ≥10) are shown in Table III. The sensitivity and PPV of the radiological and surgical assessment of PCI score was low while specificity and NPV of these methods were above 85%. However, diagnostic accuracy of both assessments of PCI was also above 80%.

Morbidity during surgery was reported in 5 (19.2%) cases. These five cases included one with a bowel, one with a vascular, one with an ileostomy, and one with a colostomy damage.

DISCUSSION

Ovarian cancer ranks 7th in terms of the total cancer prevalence and 8th in terms of cancer-related mortality among women. Each year, 240,000 women worldwide receive an OC diagnosis; with a five-year survival of less than 45%, the disease accounts for 150,000 deaths worldwide.[1,14] Most malignancies in women under 40 are germ cell tumours, and OC is uncommon in this age range. Over 90% of tumours are epithelial, and the risk rises with age, reaching a peak in the late 70s. When ovarian cancer is diagnosed, it often progresses across the abdomen and has peritoneal carcinomatosis. Primary surgery with the goal of total cytoreduction is the cornerstone of treatment and is followed by chemotherapy. Due to the disease's broad nature, surgery is frequently involved and not appropriate for all individuals. Identifying patients with non-resectable tumours who would benefit most from neoadjuvant therapy is crucial.[3,7,15]

The PCI is utilised intraoperatively to assess the spread of tumour in the abdominal and pelvic regions.[7,10,14] It has been discovered that the PCI, which has been employed for a thorough assessment of the peritoneal dissemination in gastrointestinal tumours, is a prognostic predictor of survival.[16] When Jacquet and Sugarbaker initially presented the PCI in 1998, it was widely accepted as the standard method for characterising mesothelioma and carcinomatosis of colorectal cancer.[10,12,13,17,18]

A study investigating the predictive value of PCI in OC patients, found a negative association between a high PCI score and survival. Preoperative CA125 concentration, ascites presence, longer surgery duration, FIGO stage, positive para-aortic lymph nodes, longer hospital stay, number of bowel and other visceral resections performed per patient, operative and postoperative complications, and suboptimal resection of tumour were significantly correlated with PCI according to Llueca *et al.*[13] Tentes *et al*. studied the prognostic significance of PCI in 60 AOC patients.[16] They found that patients with PCIs of ≤10 and >10 had distinct 5-year survival rates (65% *vs*. 29%) and a 51% optimal cytoreduction rate.

One established predictive measure for the operability of OC is PCI.[14,19] However, the location of the cancer has a significant role in determining surgical operability in addition to the tumour burden. Patients are often rendered inoperable due to massive small bowel invasion. Previous research has demonstrated that the small bowel is the most challenging region to evaluate carcinomatosis using radiography. According to a research,[8] PET/MRI had a greater sensitivity for small intestinal carcinomatosis than DW-MRI alone. The total PCI, as measured by PET/MRI and DW-MRI, showed a strong correlation with surgical PCI, the gold standard. The PCI calculated from DW-MRI and PET/MRI showed a strong favourable correlation with surgical PCI ($\beta = 0.86 \pm 0.14$ $p < 0.01$, $\beta = 0.94 \pm 0.01$ $p < 0.01$). The mean difference in agreement, or bias, between DW-MRI and PET/MRI was somewhat greater in the Bland-Altman plot, but the difference was not statistically significant. In few areas, DW-MRI's specificity exceeded PET/MRI's, ranging from 50 to 100% for both methods.

In a recent study,[20] 188 patients with serous high-grade OC were included in the analysis of the predictive and prognostic significance of PCI with respect to complete cytoreduction and clinical consequences. According to their findings, PCI was a good indicator of full cytoreduction (ROC analysis, AUC 0.8227). Higher PCI scores were correlated with poorer 5-year overall survival ($p < 0.001$) and 5-year disease-free survival ($p < 0.001$) in patients having greater degree of cytoreduction.

The PCI score was linked to clinical outcomes and showed a high degree of prediction for full cytoreduction. Poorer survival was correlated with higher PCI scores in the context of severe complications. Therefore, in instances when full cytoreduction is regarded possible, it is crucial to minimise significant perioperative problems in patients with large tumour loads.[20]

According to a research, ROCs were used to identify the predictors for incomplete cytoreductive surgeries (CRS).[7,8] Based on these studies, the intraoperative PCI score (AUC = 0.945) was the greatest predictor of partial CRS. According to Di Donna *et al.*[21] the laparotomic PCI confirmed an AUC =

0.83, demonstrating the best performance in predicting residual disease. In contrast, the radiological and laparoscopic PCI showed AUC = 0.64 and AUC = 0.73, respectively. Fagotti *et al*. introduced a laparoscopic model that uses a score system ranging from 0 to 12 based on six variables.[22] This model accurately identified suboptimal CRS for scores ≥8 with 100% specificity and positive predictive value (PPV), and 70% negative predictive value (NPV). The laparoscopy-based score of 8 was found to be associated with suboptimal surgeries with a sensitivity of 46%, specificity of 89%, PPV of 89%, NPV of 44%, and accuracy of 60%.[22-24]

According to Avesani *et al.s*' study, there was a meaningful correlation between CT-PCI and the likelihood of postoperative residual disease (OR 1.04, 95% CI 1.01–1.07; p = 0.003).[25] Patients with residual disease following surgery had a median CT-PCI of 16 (interquartile range, IQR 6-20), whereas patients who had successful CRS had a median CT-PCI of 7 (IQR 0-19). Patients with PCI >16 accounted for 32% (31/97) of the unsatisfactory cytoreduction patients, while patients with PCI <16 accounted for 18% (32/180) (p = 0.001). The area under the ROC curve was calculated to be 0.63 with a 95% confidence interval ranging from 0.56 to 0.71. The highest PPV for thorough resection was 0.36, conforming to a PCI threshold of 9, and the highest NPV was 0.90, conforming to a PCI threshold of 16.

Lomnytska *et al.* found that a PCI value of 21 or above was an independent predictor of severe complications after surgical treatment for ovarian cancer.[9] Increased PCI negatively impacted overall survival, although high-grade comorbidities did not affect the overall survival.

This study revealed an interclass correlation of 0.52 (95%CI: 0.17-0.75) between radiological and surgical PCI. The agreement among the PCI scores is shown in the Bland-Altman plot with a bias of 1.115 ± 1.96 × 4.61. Ninety percent of individuals with a PCI score below 10 showed no remaining disease upon surgical assessment. The mean length of operation and blood loss were significantly less in patients with a PCI score of less than 10 compared to those with a score higher than 10. Patients with a PCI score of less than 10, experienced a lower rate of complications.

This study had some limitations. First, this was a small population of only 26 individuals, therefore, the findings must be evaluated in that context. Second, the data were collected from a single centre, for this prospective cross-sectional study, which may have influenced the findings. Nonetheless, it is impossible to determine the direction of causality between pairs of factors.

CONCLUSION

Prior to surgery, PCI was proven to be a very useful non-invasive method for predicting residual disease and operability; higher tumour load was associated with additional challenges. When deciding when to have surgery, it can be of great benefit. For patients with advanced ovarian cancer, the PCI score is a valid means for evaluating the intraoperative disease state. In the clinical care of advanced gynaecologic malignancies, the authors advise using the PCI as a standard measure.

ETHICAL APPROVAL:
An approval for the study was obtained from the Aga Khan Ethics Committee (ERC #: 2021-6476-18811).

PATIENTS' CONSENT:
Informed and written consent was obtained from the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HA: Conception, design, data collection and statistical analysis, and manuscript writing.
ABA: Statistical analysis, manuscript writing, editing, and responsible for all aspects of the research in ensuring that questions related to the accuracy of the data are resolved and available for any future correspondence.
UC, IM: Data collection, and manuscript writing.
All authors approved the final version of the manuscript to be published.

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