



Clinico-pathological outcomes after total parietal peritonectomy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in advanced serous papillary peritoneal carcinoma submitted to neoadjuvant systemic chemotherapy- largest single institute experience

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ABSTRACT

Introduction: Serous papillary peritoneal carcinoma (SPPC) is a rare clinical entity. Based on the understanding of the pattern of spread, its multifocality, polyclonality and the high frequency of diffuse, widespread peritoneal metastasis, a robust rationale for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for SPPC exists. Herein we report the clinical outcomes of SPPC patients treated with neoadjuvant systemic chemotherapy (NACT) followed by CRS including total parietal peritonectomy and HIPEC.

Methods: Clinico-pathological data of 22 patients of serous papillary peritoneal carcinoma (SPPC) was retrospectively analyzed from a prospectively maintained database from June 2000 to July 2017. Patients were treated with CRS, total parietal peritonectomy and HIPEC with cisplatin (42 mg/L of perfusate) and doxorubicin (15 mg/L of perfusate) after NACT. Survival curves were calculated from the date of surgery.

Results: 22 patients underwent CRS, total parietal peritonectomy and HIPEC. The median age was 62 years (Range 47–72). On histological evaluation, 18/30 (60%) parietal peritonectomy specimens showed microscopic disease, when no disease was evident macroscopically at surgical exploration. Grade III-IV surgical complications were recorded in 4/22 (18%) patients. There was no postoperative mortality. At a median follow up of 12 months, the five-year overall survival (OS) was 64.9%. The median OS was not reached. Median progression-free survival was 32.9 months and progression-free survival at 5 years was 33.2%.

Conclusion: CRS with total peritonectomy + HIPEC after NACT, presents as a promising treatment modality for SPPC, and could be associated with good survival results in patients with SPPC.

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Introduction

Serous papillary carcinoma of peritoneum (SPPC) is a rare disease entity with clinical presentation similar to primary ovarian serous papillary carcinoma [1]. The clinical entity was first described by Swerdlow in 1959 [2]. Diagnosing SPPC is a challenge as, most patients, present with diffuse peritoneal spread without

any apparent disease in the ovaries. This is seen in 10–20% cases wherein the diagnosis is SPPC and not epithelial ovarian carcinoma (EOC) [3–5]. In the absence of established standard treatment, serous papillary peritoneal carcinoma patients have been managed with cytoreductive/debulking surgery and platinum and taxane based chemotherapy, similar to epithelial ovarian cancer [6,7].

SPPC like EOC, for much of its natural history remains confined to the peritoneal cavity, which makes it a suitable target for locoregional therapies. Over the past two decades a new therapeutic strategy to treat peritoneal carcinomatosis (PC) has developed, combining optimal cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). Promising results have been obtained when this combined treatment has been applied to treating carcinomatosis of non-gynaecological origin such as pseudomyxoma peritonei, peritoneal mesothelioma and peritoneal metastasis from colorectal cancer [8–13]. Encouraging reports from several nonrandomized studies and case series have shown improved survival with the use of HIPEC in ovarian cancer [14–17]. Recently, the results of a phase three randomised controlled trial has shown a survival benefit in patients receiving HIPEC in addition to cytoreductive surgery after neoadjuvant chemotherapy in advanced stage III ovarian cancer [18].

Based on the understanding of the pattern of spread and the high frequency of diffuse, widespread peritoneal metastasis of SPPC [19], a robust rationale for cytoreductive surgery and HIPEC exists. Currently however, there is a paucity of literature regarding long term results of SPPC treated by CRS and HIPEC. Most reported series are small, either case reports or usually combined with EOC in data analysis.

We therefore report the early and long term results of a selected cohort of SPPC patients treated with neoadjuvant chemotherapy (NACT) followed by cytoreductive surgery, a total parietal peritonectomy and HIPEC. The ultimate aim of this study was to critically analyse and validate our aggressive surgical and locoregional approach in the management of this rare disease.

Materials and methods

Patient population: This is a retrospective study of a prospectively maintained database. Between June 2000 and July 2017, 29 patients were diagnosed with SPPC, out of which 22 patients underwent CRS with total peritonectomy and HIPEC in our institute. The present study received IRB approval. Ours being a tertiary referral centre, these patients had already received some form of initial surgical treatment and/or biopsies at another centre and were then referred to us for second opinion and further management. All patients presented with advanced peritoneal disease without any evidence of extra abdominal metastasis. The extent of previous surgical intervention was calculated as per the prior surgical score (PSS) [13]. The prior surgical score (PSS) quantitates the extent of surgery prior to definitive combined treatment. For a PSS of 0: no prior surgery or only a biopsy was performed; PSS of 1: indicates one region with prior surgery; PSS-2: indicates 2 to 5 regions previously dissected; PSS-3: indicates more than 5 regions previously dissected. The histopathological slides of all patients were reviewed by an expert pathologist from the institute. Clinical diagnoses of SPPC was made according to the Gynecologic Oncology Group recommendations [5].

1. Ovaries of normal size or enlarged by a benign process.
2. Absent ovarian involvement or limited to the surface and/or superficial cortex with no tumor nodule within the ovarian cortex exceeding 5x5 mm
3. Serous histology

4. Volume of extra-ovarian disease which significantly exceeds that of ovarian disease.

Treatment: Once the diagnosis of SPPC was established and confirmed, all patients received preoperative doublet neoadjuvant chemotherapy (NACT) with cisplatin/carboplatin and paclitaxel. All patients received a total of 6 cycles of NACT prior to cytoreductive surgery. Following chemotherapy, patients were evaluated with thoracic and abdominal contrast enhanced tomography and serum tumor marker measurements. Patients with stable disease or partial response were then selected for CRS + HIPEC. 7/29 patients were excluded from CRS + HIPEC as 5 patients had progressive extra abdominal disease after NACT and 2 patients had poor performance status. Hence 22/29 patients were treated with CRS which included a total parietal peritonectomy, in all cases and HIPEC. At laparotomy, the extent of disease was evaluated using the peritoneal carcinomatosis index (PCI). At cytoreduction, a total parietal peritonectomy was performed in all patients irrespective of the chemo response. The total parietal peritonectomy was categorized as right diaphragmatic peritonectomy, left diaphragmatic peritonectomy, anterior parietal peritonectomy, pelvic peritonectomy, greater omentectomy and lesser omentectomy. The macroscopic presence of disease in each of these areas of the peritoneum was recorded. After cytoreductive surgery, the pathological examination of the resected specimen was evaluated as per the same categories to evaluate for microscopic residual disease irrespective of the presence of gross visible disease. Visceral resections were performed as deemed necessary to achieve a complete cytoreduction. Systematic pelvic and retroperitoneal lymph node dissection was performed in all except four patients. The technique of peritonectomy performed was as described by Sugarbaker [8]. Completeness of surgical cytoreduction (CCR) was classified as CCR-0: macroscopically complete; CCR-1: residual disease <2.5 mm; or CCR-2: residual disease >2.5 mm [13]. After complete cytoreduction, closed-abdomen HIPEC was performed at 42.5 °C with cisplatin (43 mg/L) plus doxorubicin (15 mg/L) for 90 min for 90 min. Perfusate volume was 2.5 L/m². Post operative complications were graded according to the serious adverse events score (NCI-CTCAE version 4). We performed a surgical histological correlation study considering the following intra abdominal regions that were deemed intraoperatively not involved by the surgical team: right diaphragmatic peritoneum, left diaphragmatic peritoneum, pelvic peritoneum, greater omentum, and lesser omentum. The pathologist analyzed these regions separately starting with a gross macroscopic evaluation and selection of suspicious areas for sections for H&E. Then he randomly selected other three non suspicious areas for additional sections. Results of the intraoperative findings (negative) were confronted with the histological report (negative/positive). Postoperative follow-up comprised of physical examination, thoracic and abdominal contrast enhanced tomography and tumor marker measurements every four-months during the first 2 years and six-monthly thereafter.

Statistical analysis: Overall Survival (OS) was calculated from the date of CRS + HIPEC to the date of death or last follow up and Progression free survival (PFS) was determined from the date of CRS + HIPEC to the date of first recurrence. Survival curves were calculated using the Kaplan–Meier method and compared using the two-tailed log-rank test. Descriptive variables were analyzed using nonparametric tests, χ^2 -test for categorical variables and Mann-Whitney-U test for continuous variables. All statistical tests were two sided, with the significance level established at p -value of <0.05. All statistical analyses were conducted using SPSS version 18.0.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient and treatment characteristics

Seven out of twenty-two patients were excluded from CRS + HIPEC as 5 patients had progressive extra abdominal disease after NACT and 2 patients had poor performance status which precluded any surgical intervention. Hence 22/29 patients were treated with CRS which included a total parietal peritonectomy, in all cases and HIPEC Clinical characteristics of 22 patients who underwent CRS with total peritonectomy and HIPEC is outlined in Table 1. All 22 patients were female with a median age of 62 years (Range 47–70). The prior surgical score (PSS) was 1 in 50% (11/22) of patients (Table 1). The median PCI was 10.5 (Range 1–31). A systematic pelvic and/or retroperitoneal dissection was performed in all except 4 patients (Table 1). 45.5% (10/22) patients were found to have positive lymph nodes. The extent of surgical procedures performed is summarized in Table 2. At the completion of cytoreductive surgery, 15/22 CCR-0 resections (68.2%) and 07/22 CCR-1 resections (31.8%), were recorded. In 18/30 (60%), peritonectomy specimens categorized as above, pathologic examination revealed microscopic residual disease, when surgical exploration showed no evidence of macroscopic disease (Table 3). The pathological complete response rates was 9% (2/22). The median operating time was 554 min (Range 400–660).

Morbidity and mortality

The median hospital stay was 24.5 days (Range 13–72). Overall, grade III-IV surgical complication was seen in 4/22 (18%) patients (Table 4). Anastomotic dehiscence was seen in 1 patient with a ileocolic anastomosis. Postoperative ureteric stenting was required in two patients with ureteric fistulae. Grade III-IV Hematological toxicities were seen in two patients. One patient developed severe neutropenia and circulatory shock with respiratory distress. There were no post operative mortality.

Survival

Survival analyses were performed in 22 patients. At a median follow up of 12 months, the five year overall survival (OS) was 64.9%

Table 2
Details of Surgical procedures.

Procedure	N
Peritonectomy	
Diaphragmatic(Left + Right)	22
Glissonian Capsule	6
Lesser Omentum	22
Greater Omentum	16
Pelvic Peritoneum	22
Other Surgical Procedure	
Gastro Intestinal Resections	28
Gastro Intestinal Anastomosis	12
Splenectomy	19
HysteroSalphingo-Ophorectomy	12
#Other Procedures	25

*(Diaphragmatic Resection, Cholecystectomy, Appendectomy).

(Fig. 1).The median OS was not reached. Median progression-free survival was 32.9 months and progression-free survival at 5 years was 33.2% (Fig. 2).

Discussion

Despite similarities between serous papillary peritoneal carcinoma (SPPC) and epithelial ovarian carcinoma (EOC), a few differences between the two exist. A recent systematic review has highlighted a few epidemiological, clinical, and molecular differences [19]. The estimated incidence of SPPC is unclear but is reported to be 10% in some series and 6.78 cases per 1,000,000 individuals in the United States [4,20]. The peak incidence of epithelial ovarian carcinoma has been reported to be at age 55–60 years. SPPC most commonly is seen in older women, an average 3–7 years older than EOC [21,22]. In our study, the median age of presentation was 62 years which coincides with the available literature. There are some fundamental differences in the tumorigenesis and pathogenetic presentation between SPPC and epithelial ovarian cancer. Firstly, SPPC tends to show a more diffuse micronodular pattern of spread in the omentum and peritoneal surfaces suggesting that SPPC is a more aggressive malignancy and is more likely to have widespread disease at the same stages of ovarian cancer. Secondly, several investigators have demonstrated that different genetic events take place at different peritoneal sites

Table 1
Clinicopathological Characteristics of patients undergoing CRS + HIPEC.

Variables	Categories	(n = 22) (%)
Median Age (Range)		62years (47–30)
ECOG	0	21(95.5)
	1	01(4.5)
Median post chemotherapy Pre-operative Serum Tumor markers (Range)	Ca 125(u/ml)	16.1(7.4–216)
	CEA(ng/ml)	1.3(0–13.3)
	Ca 19.9(u/ml)	13.1(3.30–40.4)
	Ca 15.3(u/ml)	25.7(11.5–784.4)
Prior Surgical Score(PSS)	0 = Laparoscopy + biopsy	5 (22.7)
	1 = Hystero salpingo ophorectomy + peritoneal biospies	11 (50%)
	2 = Hystero salpingo ophorectomy + omentectomy + peritoneal biospies	6 (27.3)
Completeness of Cytoreduction(CCO)	CC0=No residual tumor	15 (68.2)
	CC1 = tumor<0.25 mm	7 (31.8)
Lymph Nodes	Not Dissected	4 (18.2)
	Positive	10 (36.2)
	Negative	8 (45.5)
Tumor Grade	G1	0
	G2	7 (31.8)
	G3	11 (50)
	Not known	4 (18.1)
Median PCI(Range)		10.5 (1–31)
Median operating time(Range)		554 min (400–660)

*Platin + Taxanes.

Table 3

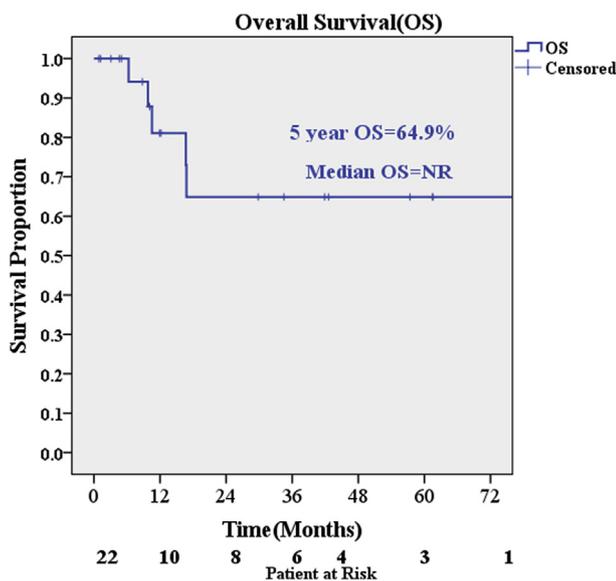
Resected specimens with Microscopic disease at pathological evaluation but no Gross residual disease at Surgery.

Resected Parietal Peritoneum Specimens Evaluated	No macroscopic Disease at Surgical Exploration (n = 30)		
	Pathological Evaluation		Total
	Microscopic disease	No microscopic disease	
Right Diaphragmatic peritoneum	6 (67%)	3 (33%)	9
Left Diaphragmatic peritoneum	3 (60%)	2 (40%)	5
Pelvic Peritoneum	0 (0%)	2 (100%)	2
Greater Omentum	2 (50%)	2 (50%)	4
Lesser Omentum	7 (70%)	3 (30%)	10
Total	18 (60%)	12 (40%)	30

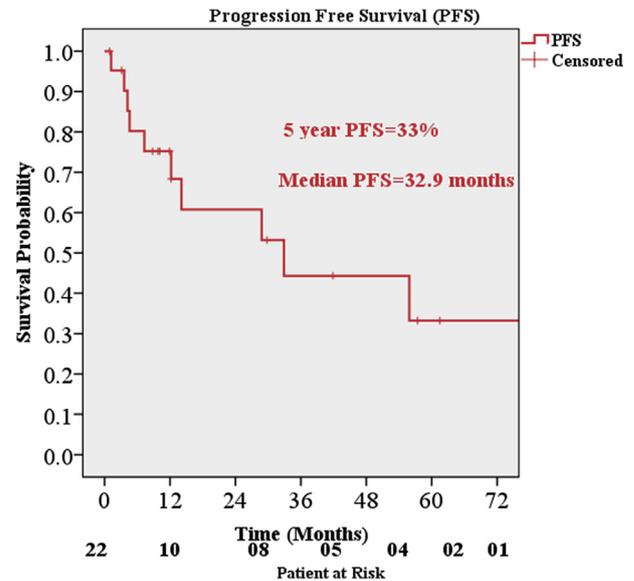
Table 4

Morbidity.

Variables	Categories	(n = 22) (%)
Median Hospital stay(Range)		24.5 days (13–72)
Surgical Complications		4(18%)
Type of Complications	Anastomotic Dehiscence	1
	Ureteric fistula	2
	Post operative Hemorrhage	1
	Grade 3/4 Hematological Toxicity	2

**Fig. 1.** Overall survival.

in the same patient, explaining the multifocality of SPPC. This means that the tumor cells present at multiple peritoneal sites within the same patient may have a different genetic make-up and clonality and may have the ability to give rise to independent primary neoplasia at multiple anatomic sites, unlike ovarian cancer which is unifocal [19,23–25]. This inherent multifocality and polyclonality of SPPC may therefore necessitate more radical peritonectomy. In order to improve the rates of optimal cytoreduction, neoadjuvant chemotherapy (NACT) has been recommended by several authors both, for SPPC and EOC [26–29]. Whilst it is common practice to perform a selective peritonectomy and resect only sites of gross residual disease as part of cytoreductive surgery, in ovarian cancer after neoadjuvant chemotherapy, the same cannot be applied to SPPC owing to its multifocal predisposition. A total peritonectomy should be performed in such regions as it has the benefit of removing both microscopic residual disease and stem cells that can

**Fig. 2.** Progression free survival.

be present in scar tissue/normal peritoneum that was previously affected. Though epithelial ovarian cancer and SPPC are chemosensitive, the chemotherapy response is sustained only in 8–10% of the patients and if the peritoneum is not removed, the tumor will invariably recur at the same site. Leaving behind any amount of microscopic disease poses the risk of recurrence as residual disease following chemotherapy can contain chemotherapy resistant cells. Second, when there is only scar tissue at previous disease sites (no obvious residual tumor) or the peritoneum is completely normal, a visual examination cannot predict the presence or absence of tumor in scar tissue and frozen section is not accurate. In our study, in 60% of the resected parietal peritoneal specimens, microscopic residual disease was present despite grossly normal appearing peritoneum at surgical exploration which further strengthens the case for a total peritonectomy. The median PCI at the time of cytoreductive surgery was 10.5 (range 1–31), which indicates at least a moderate extent of peritoneal carcinomatosis, if not greater. Our study also reported a high rate of lymph nodal involvement. In fact, 46% of patients had lymph node metastasis in both retroperitoneal and pelvic lymph nodes. Similar rates of lymph node (20%–70%) and visceral/extraperitoneal spread (<15%) have been reported in SPPC and EOC. Although not in line with the recently published randomised data in epithelial ovarian cancer on lymph node systematic dissection, by Harter [30], we propose (advisable, not mandatory) the systematic lymph node dissection in SPPC due to two reasons: 1) we claim that SPPC is biologically a distinct entity as compared to epithelial ovarian cancer (EOC), so that the recommendations established for EOC should not be extrapolated to SPPC

in every clinical circumstance; and 2) once the patient is submitted to extensive surgery associated with HIPEC, eventual lymph node recurrence would be hard to be treated surgically in the future due to postoperative adhesions. The prognostic implications of positive nodal status in both histologies is debated [31].

Most available evidence in literature reports survival and prognosis of patients with SPPC after cytoreductive surgery/debulking alone. The median survival, ranging from 10 months to 40 months is anything but modest. Coupled with this is the fact the SPPC is associated with poor prognosis and earlier recurrences [22,32–36].

There is evidence to suggest that SPPC shows reduced sensitivity to chemotherapy and increased risk of platinum resistance [24]. This further makes a case in point for the use of HIPEC after cytoreductive surgery in SPPC.

Up to date, very limited evidence for the treatment of SPPC with CRS + HIPEC exists as most cases of SPPC are included in data analyses with EOC. This makes our study, one of the largest single institution series of advanced SPPC treated with CRS + HIPEC. Secondly, in our study, cytoreduction included a total parietal peritonectomy after NACT instead of only resecting only areas of gross residual disease, which is a different approach to that used to treat EOC after neoadjuvant chemotherapy. Most recently, Bakrin et al. [37] reported the results of a multi-institutional study of 36 patients of SPPC treated by CRS with HIPEC. This study reported 5 year OS of 57.4% and a median DFS of 16.7 months and a 5 year DFS of 24%. Their study found PCI as the only prognostic factor affecting survival on univariate analysis ($p = 0.03$). In our study, the five year overall survival (OS) was 64.9% and the median progression-free survival was 32.9 months and progression-free survival at 5 years was 33.2%. Since at the time of analysis more than 50% of our patients were alive, median OS was not reached. In our study, survival analyses were performed from the date of surgery and not from initial diagnosis and so may well underestimate survival. However we failed to identify any significant prognostic factors influencing survival on both univariate and multivariate analysis. A possible explanation for this could be small number of carefully selected cases. Our study has by far, demonstrated a better OS and PFS in patients with SPPC when treated with CRS + HIPEC as compared to patients treated with cytoreductive/debulking surgery alone.

One of the reasons why clinicians are skeptical in adopting CRS + HIPEC routinely is owing to the concerns of morbidity and mortality the combination of the procedures exposes the patient to. The overall surgical morbidity rate in our study was 18%. However there was no mortality reported in our study. The morbidity rates in our study is comparable to the morbidity rates of 12%–52% reported in literature for CRS + HIPEC [38].

SPPC is a distinct disease entity and therefore must be treated with approaches different to that for treating EOC. Recent studies have shown that despite similarities in histology and response to treatment, SPPC is associated with widespread peritoneal dissemination, is more aggressive, more often has residual disease and has a poorer outcome compared to EOC [19,22,24,35]. Evidently, treating SPPC necessitates more aggressive peritonectomy procedures and requires radical surgical approaches and best results can therefore be obtained by physicians trained in the treatment of peritoneal surface malignancies. This explains why most patients in our study underwent only a diagnostic laparoscopy and biopsy or a minimal surgical intervention at initial surgical attempt elsewhere, and were subsequently referred to our institute for further management. Our study is the largest single institution experience of treating a rare peritoneal disease with CRS including a total peritonectomy + HIPEC and has demonstrated improved survival over conventional cytoreductive/debulking surgery for SPPC.

Conclusion: Treatment of SPPC requires aggressive surgical

approach and CRS + HIPEC presents as a promising treatment modality associated with good survival with acceptable morbidity. Our study suggests that more radical surgery comprising of total peritonectomies at sites of residual disease performed with the goal of obtaining a complete cytoreduction might be correlated with prolonged survival in patients with SPPC.

Conflict of interest statement

We declare that there are no conflicts of interest associated with this manuscript titled “Clinico-pathological outcomes after total parietal peritonectomy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in advanced serous papillary peritoneal carcinoma- Largest single institute experience” except that author Shigeki Kusamura has received research grants from Italian Association for Cancer Research (AIRC).

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