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Open Access Journal of Cancer & Oncology

Predictors of Recurrence in Peritoneal Carcinomatosis from High Grade Malignancies after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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Research Article
Volume 2 Issue 1
Received Date: December 20, 2017
Published Date: January 02, 2018
DOI: 10.23880/oajco-16000114

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Abstract

Extensive surgical procedures like Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) despite being associated with better survival in various peritoneal surface malignancies of ovarian, colorectal, appendicular cancers yet locoregional and distant recurrence has always been an important issue. The study aimed at determining risk factors for recurrence.

Keywords: Peritoneal Surface Malignancy; Peritoneal Carcinomatosis Index; HIPEC; Recurrence; Tumor Grade

Abbreviations: WBRT: Whole Brain Radiation Therapy; CRS: Cytoreductive Surgery; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; BMI: Body Mass Index; G: Grade of Tumor; PCI: Peritoneal Carcinomatosis Index; CC: Completeness of Cytoreduction score; LAR: Low Anterior Resection.

Introduction

Peritoneal surface malignancies had always been considered as a terminal disease before Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) was introduced by Sugar baker in 1995. This procedure increases disease free and overall survival in selected patient population with locally advanced disease [1]. Proper selection of the patient is the key determining factor to reduce the chances of postoperative morbidity and to improve the survival in peritoneal carcinomatosis (PC) of appendicular, colorectal and ovarian origin. Literature suggests that CRS and HIPEC can be an effective therapy to treat PC and several patients and tumor related factors such as age, sex; size and location of tumor, primary organ of origin, lymph node status and grade of tumor have important implication in the prognosis of disease and tumor specific survival. Majority of the studies also propose peritoneal carcinomatosis index (PCI) as an important predictor of DFS following CRS and HIPEC [2,3]. On the contrary, lymph node status and PCI were not considered to be the important predictor of disease recurrence [4]. The purpose of the current study was to evaluate the potential predictors of recurrence following CRS and HIPEC in patients of peritoneal surface malignancies arising from various organs.

Methods

Data were recorded from prospectively maintained computerised database and analysed at All India Institute

of Medical Sciences in the department of Surgical Oncology between 2014-2017 and ninety seven patients were enrolled.

Results

All ninety seven patients underwent the surgical procedure of CRS and HIPEC. Median follow up was 237 days (range: 64–1,080) and median time to recurrence was 182 days (range: 107- 543). Fifty six (57.73%) patients were found to develop recurrence in the defined follow- up period. Univariate and multivariate analysis were performed to determine the risk factors for recurrence. High tumor grade [(G: 3); p = 0.0004] and high peritoneal carcinomatosis index [PCI; p= 0.037] as an independent risk factors for recurrence and serous and signet ring cell adenocarcinoma ovary also showed a statistically significant trend for recurrence (p = 0.0031).

Conclusion

Primary histopathological tumor grading, high PCI , serous and signet ring cell adenocarcinoma appears to be an independent risk factor for distant systemic as well as loco-regional recurrence following optimal CRS and HIPEC in peritoneal surface malignancies.

Methods

Study Design

This was a prospective study where patients were followed in postoperative period and all the complication (which occurred within 30 days of the surgery) was recorded and the rates of mortality were also documented.

The data of patients were collected from prospectively maintained database of ninety seven patients (N=97) who were treated with CRS/HIPEC for PC between October 2014 and July 2017. The purpose of the current study was to identify the factors which could have implications in locoregional and distant recurrence following CRS and HIPEC.

Patient Selection

CRS and HIPEC is a challenging procedure involving extensive surgical resection and appropriate patient selection is an important step in this procedure. In current study, patients with PC from ovarian cancer, colorectal cancer and appendicular cancers were included. Patients with disseminated extra-abdominal metastatic disease (involvement of liver parenchyma, pulmonary and brain metastasis, or bone involvement) and performance status of Eastern Co-operative Oncology Group (ECOG ≥ 2) were excluded from the study. Conventional computed tomography (CT) scan of the chest, abdomen, and pelvis, as well as tumor markers (CEA, CA19-9 and CA-125) were obtained prior to CRS and HIPEC.

CRS /HIPEC and Postoperative Complications

For, the purpose of the study, the entire cohort was subdivided as low tumor loads, where PCI <15 and high tumor loads with PCI>15. Standardised surgical resections were performed to achieve optimal cyto reduction (CC: 0–1), which was defined as no visible tumor nodules or nodules less than 2.5 mm in size. All the patients were operated with open colesium technique with the intent of complete CRS and HIPEC using Sugarbaker's peritonectomy procedures [5]. Surgical complications were defined and graded according to Clavien Dindo's Classification of Surgical Complications [6]. Patients were followed up at three monthly intervals with tumor markers and clinical examination. Imaging was done for patients in follow up who either presented with raised tumor marker or those who had positive findings on clinical examination suggestive of recurrence.

Statistical Analysis

Recurrences were calculated as the time from CRS/HIPEC and the first sign of recurrence including biochemical relapse and/ or imaging detected recurrence. Data are mentioned as median and n (%). Risk factors for recurrences were assessed by univariate (log rank test) and multivariate (cox-regression test) analysis. All analyses were performed using STATA (Version: 14) and $p<0.05$ classified as statistically significant correlation throughout the study.

Results

Demographic Characteristics

Clinical characteristics were listed in Table 1. Where CRS/HIPEC was performed in ninety seven patients. Median age of the cohort was 57 years (range: 25 -65) and M: F ratio was 1: 2.34 where females comprised 70% of the study population. Median body mass index (BMI) was 27.12 (range: 25-39). In current study, ovarian cancer comprised of 58.76%, colorectal cancers constituted 32% and appendicular cancer accounted for 9.28%.

Characteristics	n (%)
Male/Female	29/68 (30%/ 70%)
Age	57 (25 – 65)
Body Mass Index BMI (m/kg^2)	27.12 (25-39)
Primary organ of origin	
Ovary	57 (58.76)
Colon and rectum	31(32)
Appendix	9 (9.28)
Tumor characteristics	
Histological grade of primary tumor	
G=3, high grade	76 (78.35)
G ≤ 2	21 (22)

Table 1: Demographic characteristics

Perioperative and Postoperative Period

Intraoperatively tumor burden was calculated as peritoneal carcinomatosis index (PCI) and PCI< 15 considered as low tumor load and PCI> 15 as high tumor load. Variable extents of surgical resections were performed to achieve R_0 resection and all patients received HIPEC. Median PCI was 14 (range: 8-25), where patients with PCI<15 found in 7.21% and PCI>15observed in 92.78%. Median operating time was 581 min (range: 172- 874); median hospital stay was 7.81 days (range: 5-25). Postoperatively, 25.77% patients had Clavien Dindo grade III (major) complications (Table 2).

Characteristics	n (% or range)
Peritoneal seeding/deposits	97 (100%)
Peritoneal carcinomatosis index (PCI)	
PCI < 15	7 (7. 21%)
PCI >15	90 (92.78%)
Median operating time	581 min (172- 874)
Extent of resection	-
Right hemicolectomy + anterior parietal peritonectomy	14 (14. 43%)
LAR + pelvic peritonectomy	10 (10.30%)
Anterior resection + pelvic peritonectomy	7 (7.21%)
Total omentectomy	57 (58.76%)
Cholecystectomy	10 (10.30%)
Segmental ureteral resection	3 (3.09%)
Completion of cytoreduction (CC-0) score	
CC- 0	86 (89%)
CC- 1	7 (11.34%)
Median hospital stay	7.81 days (5-25)
Postoperative complication rate	-
Major/ ClavienDindo (Grade III)	26 (25.77%)
Clavien Dindo grade I /II	7 (7.21%)

Table 2: Perioperative and postoperative period

Follow up and Recurrence Patterns

Median follow up was 237 days (range: 64-1,080) and median time to recurrence was 182 days (range: 107-543). Patterns are listed in Table 3. Fifty six (57.73%) patients developed recurrence and 46.43% of these had intraperitoneal recurrence whereas distant systemic metastasis to lungs and brain, bone was found in 32.14%, which were later considered for palliative chemotherapy with or without external beam radiation treatment (EBRT) to bone and whole brain radiation therapy (WBRT).

Follow up and recurrence	n (%; or range)
Median follow up	237 days (range , 64-1080)
Median time to recurrence	182 days (range , 107-543)
Overall recurrence	**56 (57.74%)**
Organ of primary tumor	31/97 (32 %)
Recurrence in ovarian tumor	21/97 (21.64 %)
Recurrence in colorectum	21/97 (.64 %)
Recurrence in appendicular cancer	4 /97 (4.12 %)
Serous adenocarcinoma	31/56 (32%)
Recurrence patterns	
Distant systemic (brain/ pulmonary) recurrence	15/56 (26.78)
Distant systemic + peritoneal recurrence	3 /56 (5.36)
Isolated intraperitoneal recurrence	26/56 (46.43)
Retroperitoneal recurrence	12/56 (21.43)

Table 3: Follow up and recurrence patterns

Statistical Analysis to Predict Risk Factors for Recurrence

Log rank test in univariate analysis showed primary tumor histopathological grading (G: 3) as an independent risk factor for both locoregional and systemic sites (p = 0.028) and this observation was also correlated well with the high tumor burden disease (PCI>15; p = 0.003). Subgroup analysis for ovarian and colorectal cancer had shown that serous adenocarcinoma as an independent risk factor recurrence (p= 0.026). Multivariate analysis also confirmed high tumor grade (p= 0.0004), high PCI (p=0.037) and serous and signet ring cell histopathology as risk factors for recurrence (table 4). However, lymph node involvement did not reveal statistically significant trend (p=0.839).

Characteristics analysis	Recurrence (%)n=56/9 (57.73%)	Univariate analysis (Log-rank)	Multivariate (Cox-regression)
Age> 60	87	p=0.941	p = 0.0004
G ; 3	76	p= 0.028	p= 0.037 p= 0.037
PCI > 15	90	p= 0.003	p= 0.050
CC- 0/1	93	p= 0.050	p= 0.050
Node status (N+)	91	p= 0.839	p= 0.839
Serous and signet cells	78	p= 0.026	p= 0.026 p= 0.0031
Mucinous adenocarcinoma	19	p= 0.860	p= 0.860

Table 4: Statistical analysis for risk factors

Discussion

With the introduction of CRS /HIPEC, peritoneal carcinomatosis is now no more dealt as a terminal disease [7,8]. This is an acceptable therapeutic option for PC with reported morbidity and mortality rates at 12–67 % and 0–9 %, respectively. Proper patient selection is critical to offer best chances of cure and survival. In this study, we experienced Clavien Dindo grade III in 6.19% and two patients (2.06%) died of preoperative mortality. PC being an aggressive disease entity is poorly responsive to systemic chemotherapy. CRS/HIPEC is an important therapeutic alternative in such patients.

We analysed the data of our institution and after optimal CRS/HIPEC, 57.73% of overall recurrences were found where medina time to recurrence was 182 days which was in accordance with the other studies [9]. After CRS/HIPEC disease recurrence does not occur only in peritoneum but can also involve distant systemic sites [9,10]. High incidence of pulmonary and or brain metastasis was observed in our series. In the recent past, correlation between tumor grade and risk of developing recurrence has been established for appendicular and colorectal cancers following CRS/HIPEC and the similar results were also observed in our study [11,12]. Researchers have proposed that a high PCI is a poor predictor for disease free survival and current series also favors that high tumor burden (considered as PCI>15) and histopathological variant such as serous and signet cell adenocarcinoma as an important predictor for recurrence whereas according to some authors absolute PCI does not impact DFS.

Baumgartner et al in 2015 in their research, highlighted that the number of lymph node in high grade appendiceal and colorectal peritoneal carcinomatous influence the DFS however, our cohort doesnot favour the fact on univariate analysis. Peritoneal carcinomatosis of ovarian, colorectal or appendicular origin in present series also reflects that high lymph node positivity is not a statistically significant predictor for relapse. Peritoneal mucinous carcinomatosis not only affects overall survival but it significantly reduces the DFS as well. Authors have also suggested that high PCI, peritoneal mucinous carcinomatosis, and positive lymph node are important predictors for progression of the disease after optimal CRS/HIPEC and pathologic subtype has been suggested as the dominant factor in survival [13,14]. On the contrary, we found serous and signet cell adenocarcinoma (p = 0.026 on univariate and p= 0.0031 on multivariate analysis) as a significantly worse prognostic factor for relapse and not mucinous adenocarcinoma (p= 0.860).

Other demographic and clinical characteristics such as age, sex, BMI and primary organ of origin for peritoneal carcinomatosis do not appear to influence time to recurrence and hence survival. However, intraoperative tumor resection status, i.e; CC- O/1 could be a statistical significant parameter for recurrent disease (p= 0.050; borderline significant).

Conclusion

Despite optimal CRS/HIPEC, recurrence has always been an important concern. Primary tumor histological grade, serous and signet cell adenocarcinoma, high PCI> 15 and CC- 0/1 may be an important tool to predict relapse. Of these high tumor grades appear to the most important independent predictor for recurrence for peritoneal carcinomatosis derived from ovarian, appendicular and colorectal cancer.

Acknowledgement

The authors would like to thank M.D. Ray and S.V.S Deo for revising and editing the manuscript and Vishwajeet Singh for providing statistical analysis.

Disclosure

There are no conflicts of interest.

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