Ovarian Metastases in Colorectal Cancer and Pseudomyxoma Peritonei with peritoneal metastases.

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OVARIAN METASTASES IN COLORECTAL CANCER AND PSEUDOMYXOMA PERITONEI WITH PERITONEAL METASTASES.

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ABSTRACT

Objective: The aim of this study was to evaluate the incidence, survival data and prognostic factors in a national treatment centre for CRS and HIPEC in Norway when ovarian metastases are found concurrently with peritoneal metastases.

Methods: Between 1993 and 2012, 152 consecutive women with pseudomyxoma peritonei (PMP) and peritoneal carcinomatosis (PCA) from colorectal cancer were treated for peritoneal disease. The patients were treated radically with maximal cytoreductive surgery (CRS), followed by early postoperative intraperitoneal chemotherapy (EPIC) between 1993 and 2002, and with hyperthermic intraperitoneal chemotherapy (HIPEC) from 2003. Data regarding the patients were prospectively registered into the institutional peritoneal surface malignancy database.

Results: 152 patients were included in the study group. 42 of 65 patients treated for PCA (64,6%) had metastases to one or both ovaries at the time of surgery and HIPEC. The tumor grew infiltrating in all PCA patients. In the PMP group, 69 of 87 patients had ovarian metastases (79,3%) but fewer of these were infiltrating tumors (20,6%).
The 5-year survival rates for all radical resections were 38.3% in PCA and 85.8% in PMP. After complete surgical resection of PCA and preoperative

HIPEC the 5-year survival rate for women with confirmed ovarian metastases were 30.6% and for those without ovarian metastases 60.6% (p=0.049). The median survival time was less, 40 months in ovarian metastases whereas the median time was not reach in the group without (Figure 1). When we look at the progression free survival data in PCA we find the same with median survival times of 13 versus 28 months.

When the patients with PCA had ovarian metastases, the tumour burden measured by the PCI value was higher (12.6 versus 6.8) and operation time longer (430 minutes versus 334 minutes). However, there was no difference in days of hospital stay or in values for CEA.

There is a strong association between histopathological differentiation and invasiveness in patients with PMP with more infiltrating growth in the subgroup with peritoneal mucinous carcinomatosis

Conclusion: Ovarial metastases are associated with advanced disease and poor survival rate. The high percentage of ovarian metastases both in PCA and PMP lead to the conclusion that bilateral ooforectomy should be performed during the CRS when peritoneal metastases a Ovarian masses can represent spread from a colorectal primary tumor. Often the ovarian metastasis also is combined with peritoneal metastases. It is therefore important to evaluate the CEA, do a colonoscopy and refer the patient to evaluation for CRS and HIPEC if colorectal origin is likely. This treatment can offer the patient best chances for cure are evident, regardless of age.

INTRODUCTION

Approximately 30% of ovarian neoplasms are metastatic, and nearly half of them originate from the gastrointestinal tract[1;2]. A new pelvic mass in a woman with history of colorectal cancer is more likely metastatic (57%) than a benign (27%) or malignant ovarian tumour (16%)[3]. In a review of ovarian neoplasms in colorectal cancer the incidence of ovarian metastasis discovered at surgery or during follow-up was 0.8% - 7.4% and even higher 5%-9.7% in post-mortem studies[4].

Pseudomyxoma peritonei (PMP) of appendiceal origin are often discovered in advanced stages of disease where also the ovaries are affected. In cases with voluminous ovarian masses, the condition often is confused with an ovarian primary even though cancer markers could point to a colorectal origin.

Regarding colonic cancer, a prospective study from our institution[5] has demonstrated peritoneal metastases in 10% of women. Peritoneal carcinomatosis is usually demonstrated late in disease progression because symptoms occur at an advanced stage of disease. Ovarian metastasis and peritoneal metastasis can occur concurrently but the incidence is unknown. The exact pathogenesis of colorectal cancer ovarian metastases in unknown and both transcoelomic spread, hematogenous spread, lymphatic spread and direct extension have been discussed as possible mechanisms[4]. A single centre report from the Netherlands showed 65% ovarian metastases in

colorectal cancer (CRC) with peritoneal metastases[5;6]. Performing prophylactic ooforectomy during primary treatment of colorectal cancer has therefore been a subject of debate, and simultaneous prophylactic removal during cytoreductive surgery for peritoneal carcinomatosis recommended because of high, particularly in post-menopausal women.

Treatment has moved from palliation to aggressive treatment, and cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has become important in treatment of peritoneal metastasis from colorectal cancer[7;8] with superior results and increase in the 5-year overall survival rate from zero to more than 40% in selected cases[9;10].

The aim of this study was to evaluate the incidence, survival data and prognostic factors in a national treatment centre for CRS and HIPEC in Norway when ovarian metastases are found concurrent with peritoneal metastases.

MATERIALS AND METHODS

The Norwegian Radium Hospital is the national treatment centre in Norway for cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC); handling both pseudomyxoma peritonei (PMP) and peritoneal metastases (PCA) from colorectal cancer.

All women treated for PMP and PCA in the period from September 1993 to July 2012 were included in our institutional database MEDinsight approved by the Ethics Committee at the University of Oslo, 103 with PMP and 103 with PCA (www.medinfo.net/imi/projects/medinsight). In seven of the PCA patients the following operation could not confirm peritoneal disease and they were excluded from the study. The number of women with PMP has been stable during the period whereas an increasing number of patients with PCA have been treated after 2004. 10 patients in each group only underwent an explorative procedure due to extensive tumour burden whereas 5 with PMP and 19 with PCA underwent a palliative operation. As the study focuses on the ovarian disease, 2 with previous ooforectomy for other reasons and 1 with no available information regarding the ovaries were excluded (Table 1). The remaining 152 patients with PMP (n=87) and PCA (n=65), hereafter referred to as the study group, were treated radically with maximal cytoreductive surgery (CRS) and in most cases also perioperative intraperitoneal chemotherapy (PIC) (except 2 with PMP and 2 with PCA) for elimination of microscopic residual disease. Between 1994 and 2002, PIC was administered as early postoperative intraperitoneal chemotherapy (EPIC, n=33 with PMP, n=0 with PCA), and from 2003 as hyperthermic intraperitoneal chemotherapy in both groups. The median age was 56 years

(24-74) in PMP and 57 years (30-74) in PCA. Data regarding the patients, disease and treatment were partly prospectively registered into the institutional peritoneal surface malignancy database, partly retrospectively obtained from the patient records. Preoperative work-up was based on operative reports from referring hospital along with CT scans of chest, abdomen and pelvis. All patients were discussed in our multidisciplinary team meeting consisting of dedicated radiologists, oncologists and colorectal surgeons.

Definitions

Tumor distribution on the peritoneal surface found during CRS was classified according to peritoneal cancer index (PCI); retrospectively estimated from operative reports and CT scans before 2003 and prospectively registered thereafter. Thirteen peritoneal regions were given a score from 0 to 3 based on tumor size: 0, no macroscopic tumor; 1, tumor < 0.5 cm; 2, tumor between 0.5 cm and 5 cm and 3, tumor > 5 cm or confluent tumours[11]. After being assigned a PCI score of 0 to 39, the patients were categorized into three groups according to PCI intervals: PCI ≤ 10, PCI 11-20 and PCI ≥ 21. Patients operated in two séances were given the largest PCI score.

Residual tumor after CRS was classified using the Completeness of Cytoreduction (CC) score where CC-0 means no residual tumor; CC-1 residual tumor < 0.25 cm; CC-2 residual tumor between 0.25 cm-2.5 cm and CC-3 larger residual tumour[11]. Only CC-0 or CC-1 was defined as a curative resection.

Ovarian metastasis was defined as the presence of malignant cells in at least one of the ovaries either before or during CRS and PIC. Disease free survival is calculated as the time from CRS-PIC until time of recurrence.

Treatment

CRS was conducted with surgical resection of all tumor bearing peritoneum and necessary organ resections to remove all macroscopic tumor deposits. This included a bilateral ooforectomy in most patients. EPIC (1993-2002) was given as Mitomycin C (MMC) 10 mg/m^2 on day 1 and 5-fluoruracil (5-FU) 650 mg/m^2 on days 2-5. The drugs were diluted in 1000 ml dextrose and were contained intraperitoneally for 23 hours and followed by instillation of the next dose. For administration of HIPEC, the open Coliseum-technique was used from 2003 to 2008 when a semi-open technique was introduced[12;13].

The perfusion system is previously described[14]. The drug used for HIPEC was MMC 35 mg/m^2 (maximum dose of 70 mg), divided in three fractions; 50% at 0 min, 25% at 30 min and 25% at 60 min, and perfused for 90 min, in most cases directly following the CRS. The temperature was mean 41.0ºC.

Histopathological evaluation

All tissue samples regarding pseudomyxomas were classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA)

and an intermediate group (PMCA-I)[15]. Peritoneal carcinomatosis was classified in 3 grades; low, median and high differentiation.

Follow-up

The PMP patients attended the outpatient clinic for up to ten years, the first five years every six months and thereafter in most cases once a year. Follow-up included clinical examination, CT scans of chest, abdomen and pelvis and serum analyses of tumor markers (CEA, CA 19-9, CA 125). Local recurrence was defined as detection of tumor in the peritoneal cavity by CT scan. PCA patients were followed either in our outpatient clinic or by referring hospitals. Follow-up analysis was terminated on July 31th 2013. Date of death was obtained from the national health register.

Statistical analysis

Association between clinical-pathological data and extent of surgery in Table 2 were analyzed using the Chi-Square test (Pearson's and linear association as appropriate). Mann-Whitney test were used to test for differences between independent groups of quantitative variables. Curves of overall survival (OS) and disease-free survival (DFS) were calculated from the date of CRS and PIC with the Kaplan-Meier product-limit method, for OS until date of death and for DFS until date of first local or distant recurrence, or death. Uneventful postoperative courses were censored on July 31st, 2013 and on date of last follow-up (DFS). Differences between groups were analyzed using the log rank test. Survival is calculated from the date of cancer surgery in our

department. A two-sided p value of 0.05 or less was considered statistically significant. All calculations were performed using the Statistical Package for the Social Sciences® program, version 18.0 (SPSS GmBH, Chicago, Illinois, USA).

There is no funding source.

RESULTS

Ovarian Metastases

42 of 65 patients treated for PCA (64.6%) had metastases to one or both ovaries at the time of surgery and HIPEC. The ovarian tumour showed infiltrating growth in all PCA patients. When the patients with PCA had ovarian metastases, the tumour burden measured by the PCI value was higher (12.6 versus 6.8) and operation time longer (430 minutes versus 334 minutes). However, there was no difference in days of hospital stay or in values for CEA. More descriptive data of the patients in the study group are specified in Table 2.

In the PMP group 69 of 87 patients had ovarian metastases (79.3%) but fewer had infiltrating tumours than in patients with PCA (20.6%). PCI was higher (20.1 versus 8.7) when ovarian disease was present in PMP and median values for CEA was higher (58.9 versus 9.6) There is a strong association between histopathological differentiation and invasiveness in patients with PMP with the subgroup with peritoneal mucinous carcinomatosis (PMCA) showing more infiltrating growth ($p<0.001$) (Table 2).

Survival

The 5-year survival rates for all radical resections were 38.3% in PCA and 85.8%. The median survival times were 46 months in PCA whereas the median times were not reached in PMP. After complete surgical resection of PCA and perioperative HIPEC the 5-year survival rate for women with confirmed ovarian metastases were 30.6% and for those without ovarian metastases 60.6% ($p=0.049$). The median survival time was less (40 months)

in ovarian metastases whereas the median survival time was not reach in the group without metastases (Figure 1). When we look at the progression free survival data in PCA we find the same with median survival times of 13 versus 28 months (Figure 2).

DISCUSSION

A previous study has documented an incidence of ovarian metastases of 65% in patients with peritoneal metastases from colorectal cancer[6]. In the present study from the only treatment center for HIPEC in Norway (national cohort) we found 60% of women treated for peritoneal metastases after colorectal cancer also to have ovarian metastases and an even higher rate of 80% in pseudomyxoma peritonei. However, all patients in our study have peritoneal involvement, even though the PCI values are higher among patients with ovarian metastases.

Peritoneal carcinomatosis together with ovarian metastases is best treated by maximal cytoreductive surgery and HIPEC. Patients with colorectal cancer that present with ovarian metastases at primary surgery without other macroscopically peritoneal metastases are at risk of developing peritoneal carcinomatosis. Elias et al. therefore recommend second-look and CRS-HIPEC to patients with colorectal ovarian metastases[16].

Colorectal cancer that is metastatic to the ovaries poses a difficult problem for the clinicians. Treatment outside a colorectal cancer unit can lead to inferior treatment without resection of all peritoneal disease and possibly also without the additional benefit of intraoperative chemotherapy. Surgery in two séances has, in addition, been demonstrated inferior regarding survival[17]. Since ovarian masses can represent spread from a colorectal primary tumor, and often is combined with peritoneal metastases, it is important to evaluate the carcino-embryonal index (CEA), do a colonoscopy and refer the patient to

evaluation for CRS and HIPEC if colorectal origin is likely. This treatment can offer the patient best chances for cure.

After dedicated resection for colorectal carcinomatosis and HIPEC this study offers good results both in women with confirmed ovarian metastases and those with disease-free ovaries with estimated 5-year survival rates in one-third and two-thirds of the patients, in contrast to no long term survival after surgery and systemic chemotherapy. However, the progression-free survival in both groups is lower.

When peritoneal metastases are present in colorectal cancer and ovarian involvement was not obvious during HIPEC, one study demonstrated 40% microscopically disease in colorectal carcinomatosis, 24% in PMCA and 41% in DPAM[6]. Several studies found that, depending on age, prophylactic ooforectomy also will eliminate chances for an ovarian primary. Therefore we recommend bilateral ooforectomy in women with peritoneal metastases and colorectal cancer, irrespective of age.

CONCLUSION

Due to high incidence of ovarian metastases both in colorectal cancer with peritoneal metastases and in pseudomyxoma peritonei, a number of patients with microscopically ovarian disease and inferior prognosis in the patients, bilateral ooforectomy should be performed during the CRS when peritoneal metastases are evident, regardless of age. The patients should be treated in a center that offers HIPEC[16].

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Table 1: Flow chart of patients with peritoneal metastasis and concurrent ovarian metastasis

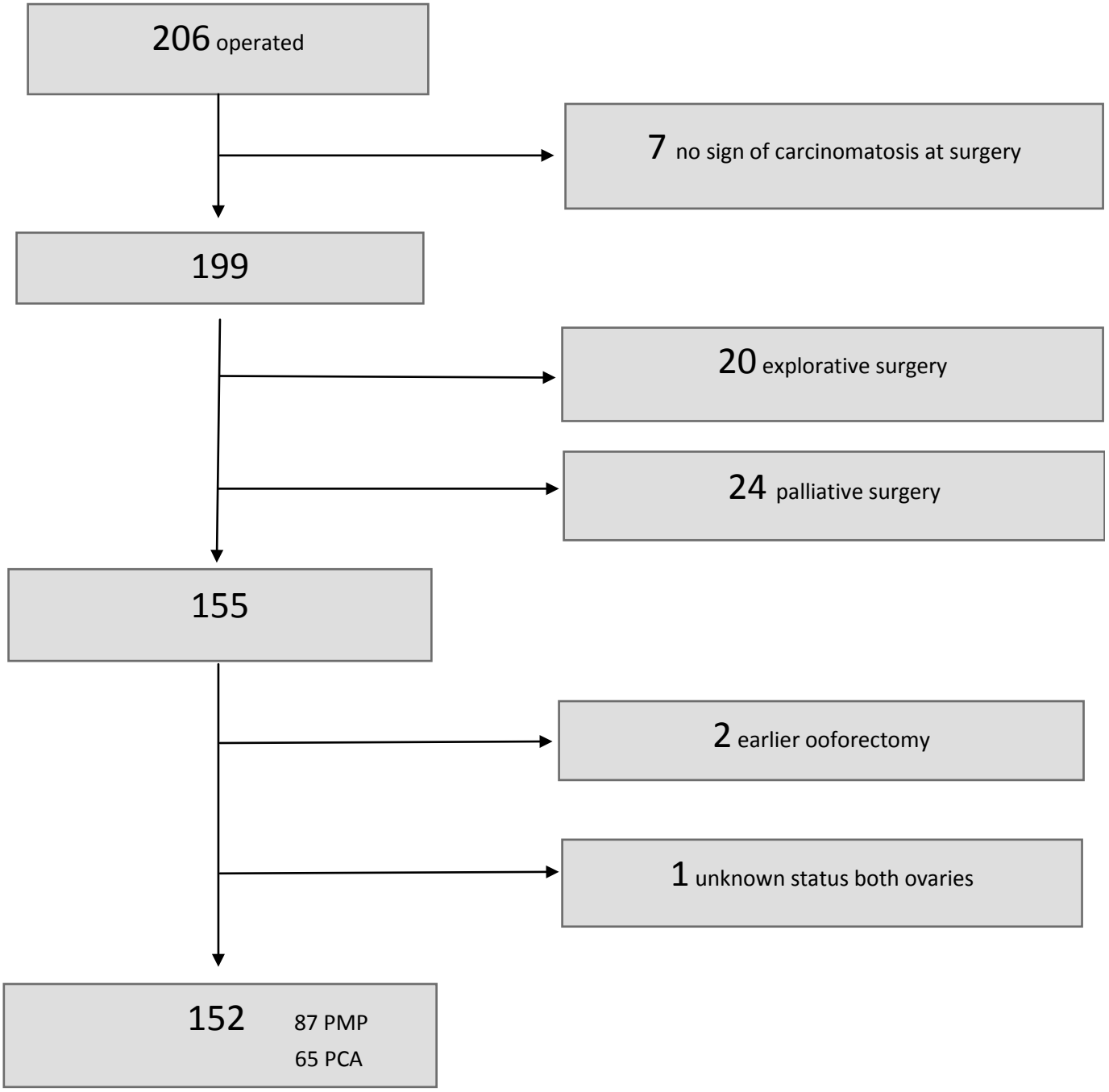
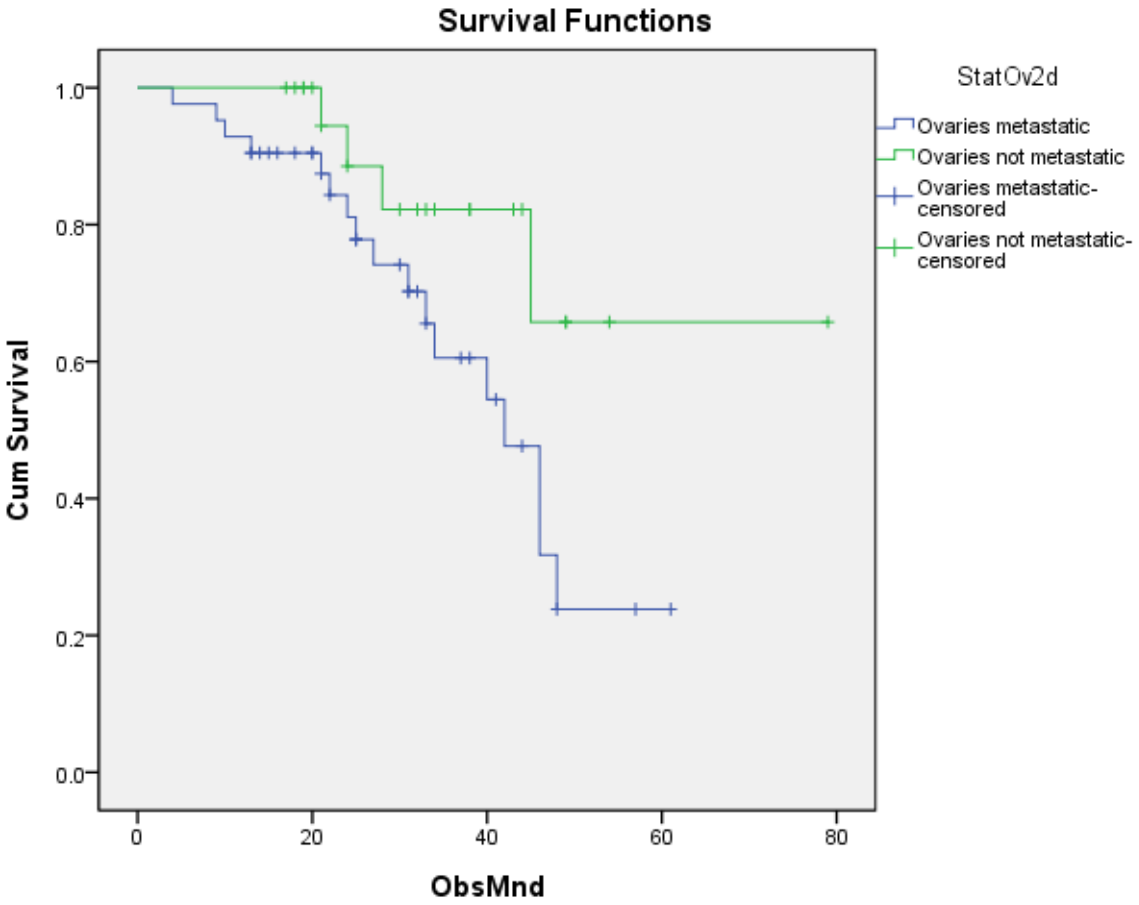


Table 2: Descriptive data in women with peritoneal carcinomatosis from colorectal cancer (n=65) and pseudomyxoma peritonei (n=87) stratified on simultaneous ovarian metastases or not

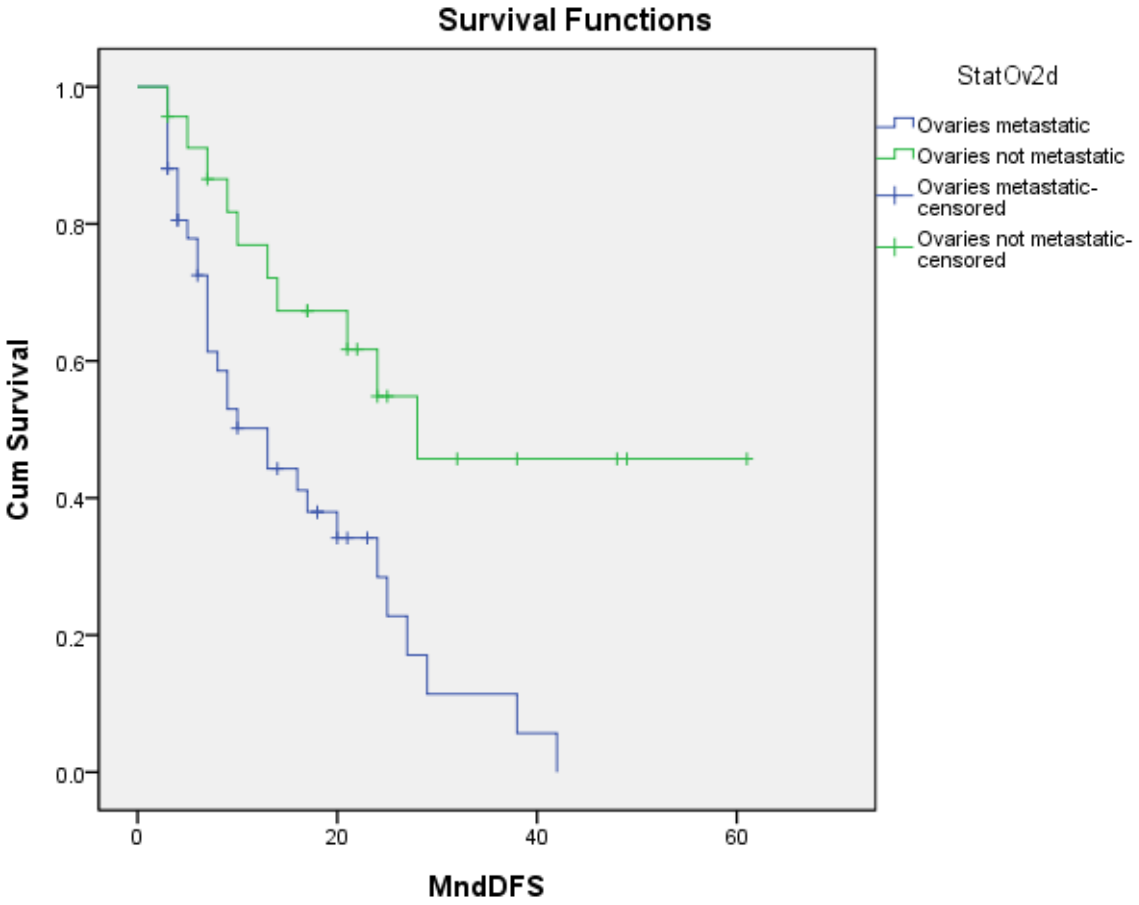
		PCA (n=65)			PMP (n=87)		
		met + (42)	Met – (23)	p	met + (69)	Met – (18)	p
age		55.64 (52.29-59.00)	53.65 (49.28-58.02)	ns	54.1(51.2-57.1)	56.5(51.0-62.0)	ns
PSS	0	6	1	ns	9	6	0.02
	1	8	8		10	6	
	2	22	12		47	4	
	3	2	1		3	2	
PCI 4 delt	0-10	19	20	0.005	16	14	<0.01
	11-20	16	3		25	3	
	21-30	6	0		23	1	
	>30	1	0		5	0	
CC	0	32	20	Analyse01	53	17	Analyse01
	1	2	0		10	0	
Infiltrating growth ovarries		42	0	0.000	18	0	0.000
CEA		108.81 (15.87-201.74)	85.21 (0-248.80)	ns	58.94 (28.71-89.18)	9.63 (1.18-18.08)	
Hospital stay		12.97 (10.00-15.95)	10.45 (8.26-12.65)	ns	19.88 (15.14-24.61)	13.33 (9.79-16.87)	ns
PCI		12.57 (10.46-14.68)	6.81 (4.66-8.96)		20.13 (17.16-23.20)	8.73 (2.77-14.68)	
PCImax		13.2 (11.1-15.3)	6.9 (4.9-8.9)		20.4 (17.5-23.3)	8.73 (2.8-14.7)	
Operation time (min)		430 (379-481)	334 (301-368)		359 (310-408)	267 (182-353)	ns
PIC	none	1	1		1	1	ns
	EPIC	-	-		27	6	
	HIPEC	41	22		41	11	
histology	high				-	-	-
	median				-	-	-
	low				-	-	-
	DPAM	-	-	-	46	13	ns
	PMCA-IM	-	-	-	10	1	
	PMCA	-	-	-	13	4	
Total survival	mnt	40	Not reached		Not reached	Not reached	ns
	% 5 year	30.6	60.6		85.4	83.3	

Figure 1: Survival in patients with peritoneal metastases from colorectal cancer stratified on women with confirmed ovarian metastases and those with disease-free ovaries



p=0.049

Figure 2: Progression-free survival in patients with peritoneal metastases from colorectal cancer stratified on women with confirmed ovarian metastases and those with disease-free ovaries



p=0.03