European Journal of Surgical Oncology 45 (2019) 2398–2404

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Pathological assessment of cytoreductive surgery specimens and its unexplored prognostic potential-a prospective multi-centric study

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ARTICLE INFO

Article history:
Received 17 June 2019
Accepted 15 July 2019
Available online 16 July 2019

Keywords:
Cytoreductive surgery
Pathological evaluation
Synoptic reporting
Pathological PCI
Lymph node metastases
Peritoneal metastases

ABSTRACT

Background and aim: The grade/histological subtype is one of the most important prognostic markers in patients undergoing cytoreductive surgery (CRS). Our aim was to study other potential prognostic information that can be derived from the pathological evaluation of CRS specimens and provide a broad outline for evaluation of these.

Methods: This prospective study (July to December 2018) included all patients undergoing cytoreductive surgery (CRS). A protocol for pathological evaluation was laid down which was based on existing practices at the participating centers and included evaluation of the pathological PCI, regional node involvement, response to chemotherapy, morphology of peritoneal metastases (PM) and distribution in the peritoneal cavity.

Results: In 191 patients undergoing CRS at 4 centers, the pathological and surgical PCI differed in over 75%. Nodes in relation to peritoneal disease were positive in 13.6%. Disease in normal peritoneum adjacent to tumor nodules was seen in >50% patients with ovarian cancer and mucinous apppendiceal tumors. 23.8% of evaluated colorectal PM patients had a complete response and 25.0% ovarian cancer patients had a near complete pathological response to chemotherapy.

Conclusions: Pathological evaluation of extent and distribution of peritoneal disease differs from the surgical evaluation in majority of the patients. Lymph node involvement in relation of peritoneal disease is common. The morphological presentation of PM in ovarian cancer and mucinous appendiceal tumors merits evaluation of more extensive resections in these patients. Standardized methods of synoptic reporting of CRS specimens could help capture vital prognostic information that may in future influence how these patients are treated.

Introduction

Cytoreductive surgery (CRS) with or without HIPEC is a potentially curative treatment for selected patients with peritoneal metastases (PM) [1]. Since the introduction of this procedure by Paul Sugarbaker, the search for prognostic factors has been an ongoing process, not only to select patients who are likely to derive

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https://doi.org/10.1016/j.ejso.2019.07.019

maximum benefit from the procedure, for surgery but also to optimize the use of systemic therapies [2]. As opposed to other sites like the lung and the liver which employ the hematogenous route, metastases to the peritoneum can result from transmesothelial, translymphatic or hematogenous spread [3]. In non-metastatic disease, for most tumors, the surgical stage is determined by the histopathological analysis of the resected tumor and considered the final stage. For patients with locally advanced disease receiving neoadjuvant therapies, the pathological stage/findings are often used to determine the need and type of adjuvant therapy.

Though in most instances, CRS is performed for stage 4 disease, the intent of surgery is cure or long term survival. However, for PM, pathological findings usually comprise of looking for the presence or absence of tumor, its histological subtype, the depth of organ infiltration and extent of regional lymph node involvement usually related to the primary tumor. The only disease that is staged based on the pathological findings is peritoneal mesothelioma [4]. Even for this disease, the peritoneal cancer index (PCI) is determined during surgery and lymph node involvement on histopathology [4].

Pathological findings can provide an accurate assessment of the extent of peritoneal disease, regional node involvement, the distribution of disease in the peritoneal cavity, patterns of peritoneal dissemination and response to chemotherapy all of which have/may have prognostic value. Currently, there are no guidelines or dataset for synoptic reporting of peritonectomy specimens [5].

This exploratory study was performed to look at the potential prognostic information that can be derived from histopathological analysis of CRS specimens. The second goal provide a broad outline for evaluation of these specimens.

Methods

This was a prospective study to which 4 peritoneal surface malignancy centers contributed. All patients undergoing cytoreductive surgery with or without HIPEC from 1st July 2018 to 31st December 2018 were included in the study. All tumors of appendiceal origin including low and high grade mucinous carcinoma peritonei, mucinous and non-mucinous adenocarcinomas were classified as appendiceal primary tumors. Mucinous peritoneal deposits from other primary tumors were included in 'rare primary tumors'.

A protocol for pathological evaluation was laid down. Institutional approval was obtained.

Surgical procedures

All procedures were performed with the goal of obtaining a complete cytoreduction (CC-0/1 resection). Standard peritonectomy procedures and visceral resections were performed [6]. Intraoperative estimation of the PCI constituted the 'surgical PCI (sPCI)'. The extent of peritoneal resection was divided into 7 peritonectomy regions that is anteroparietal, pelvic, right upper quadrant, left upper quadrant, lesser omentum, greater omentum and mesenteric peritoneum. The number of visceral resections was recorded. Structures in each region were defined using the PROMISE internet application [7]. The detailed surgical PCI included a description of the morphology of the tumor in each peritoneal region and viscera resected, the size of the largest deposit and post-chemotherapy related changes wherever applicable. Regions 5, 6, 7 were included in the 'lower region', 1,4,8 in the 'middle region' and 1,2,3 in the 'upper region'.

Pathological evaluation

The systematic protocol was based on the protocols followed at each institution. Briefly, each area of the peritoneum is marked in the en-bloc specimen or sent as a separate specimen by the surgeon. Pathologists mentioned the size of the largest tumor deposit and the presence of other small deposits in each region. One or more sections are taken from the largest nodule. Per protocol, sections are taken from at least one smaller nodule and adjacent normal peritoneum. One or more sections are taken from confluent deposits. The sub-peritoneal fat is examined for presence of lymph nodal disease. Similarly, the omenta are examined for the presence of lymph nodes. Sections are taken every 2–5 cm in absence of gross disease, however, this was not binding.

Appropriate immunohistochemistry markers are used to confirm the presence of disease in doubtful areas. The viscera resected are examined for the presence of tumor and the number and size of tumor nodules described by the pathologist. The depth of tumor infiltration is recorded, the margins and regional nodes are examined for the presence of disease. When the primary tumor is resected, the pathological evaluation is the same as that performed in absence of metastatic disease.

Nodes draining the primary tumor are regional nodes (regN) and those in relation of peritoneal deposits peritoneal nodes (perN). perN included nodes in the mesentery of resected bowel, nodes in the subperitoneal fat, paracardiac nodes, omental nodes and any other non-regional nodes that were dissected.

The pathological PCI (pPCI) was scored similar to the surgical PCI (sPCI) and the two were compared.

The evaluation of chemotherapy response is individualized according to the primary tumor site and institutional preference. At Centre Hospitalier Lyon-Sud, the classification proposed by Passot et al. is used [8]. The type of regression is further classified as fibrosis, infarct like necrosis or a colloid response. When mucin alone is present following NACT for adenocarcinomas, it is considered to be a complete response. Contrary to this, acellular mucin in appendiceal mucinous neoplasms with peritoneal dissemination is considered to be disease [9,10].

At Kishiwada Tokushukhai hospital, Osaka, Japan, the classification that has been extrapolated from the response in gastric cancer and divides the response into four categories was used [11]. At the two Indian centers, for ovarian cancer, the chemotherapy response score proposed by Bohm et al. was used [12].

The number of blocks prepared for each patient was used to determine the number of sections taken. The number of resected regions (the total number of peritonectomies and visceral resections performed) was divided by the total number of blocks to determine the sections taken from each region.

A data collection form was provided to each participating centre (supplementary material 1). Three institutions used the form, whereas, at one institution participated with their own elaborate form. The detailed pathology report was provided for all patients. All centers followed the grossing protocol with the only exception being taking sections from normal peritoneum in all regions which was followed only at one centre.

Statistical analysis

Categorical data were described as number (%). Abnormally distributed continuous data were expressed as the median and range. Categorical data were compared with x^2 test. For comparison of median values, non-parametric independent sample *t*-test and for means, independent sample *t*-test was used, where in Levene's test for equality of variance was applied. A p-value of <0.05 was considered statistically significant.

Table 1
Clinical and surgical findings in 191 patients undergoing cytoreductive surgery stratified according to primary tumor site.

Characteristic		All patients N = 191 (%)	Colorectal N = 47 (%)	Appendix N = 49 (%)	Ovary N = 44 (%)	Gastric N = 18 (%)	Mesothelioma N = 15 (%)	Rare primary N = 18 (%)	p-Value
Number of intervention	1	134 (70.1)	34 (72.4)	35 (71.4)	27 (61.3)	17 (94.4)	12 (80.0)	9 (50.0)	0.169
	2	50 (26.1)	12 (25.5)	12 (24.5)	17 (38.7)	1 (5.6)	2 (13.3)	6 (33.3)	
	>2	7 (3.6)	1 (2.1)	2 (4.0)	0 (0.0)	0 (0.0)	1 (6.7)	3 (16.6)	
Sex	Male	65 (34.0)	27 (57.4)	20 (40.8)	0 (0.0)	8 (44.4)	8 (53.3)	2 (11.1)	<0.001
	Female	126 (66.0)	20 (42.6)	29 (59.2)	44 (100.0)	10 (55.6)	7 (46.7)	16 (88.9)	
Age	<50	56 (29.3)	13 (27.6)	12 (24.5)	12 (27.2)	7 (38.8)	2 (13.3)	10 (55.6)	0.910
	>50	135 (70.7)	34 (72.4)	37 (75.5)	32 (72.8)	11 (61.2)	13 (86.7)	8 (44.4)	
NACT for PM	Received	132 (69.1)	42 (89.3)	21 (42.8)	32 (72.8)	18 (100.0)	7 (46.7)	12 (66.7)	<0.001
	Not received	59 (30.9)	5 (10.7)	19(57.2)	12 (27.2)	0 (0.0)	8 (53.3)	6 (33.3)	
HIPEC	Performed	144 (75.3)	40 (85.1)	44 (89.7)	20 (45.5)	18 (100.0)	10 (66.6)	12 (66.6)	<0.001
	Not performed	47 (24.7)	7 (14.9)	5 (10.3)	24 (54.5)	0 (0.0)	5 (33.3)	6 (33.3)	
Median surgical PCI (range)		11 [0–39]	6 [0–35]	22 [0–39]	11 [0–27]	4 [0–26]	26 [0–39]	[0–33]	
Surgical PCI	0–9	85 (44.5)	33 (70.2)	8 (16.3)	19 (43.1)	13 (72.2)	1 (6.7)	11 (61.2)	<0.001
	10–19	44 (23.0)	8 (17.0)	10 (20.4)	15 (34.0)	3 (16.6)	4 (26.6)	4 (22.1)	
	20 or more	62 (32.4)	6 (12.8)	31 (63.2)	10 (22.7)	2 (11.1)	10 (66.6)	3 (16.7)	
CC-score	CC-0	127 (66.4)	41 (87.2)	25 (48.9)	32 (72.8)	15 (83.3)	4 (26.6)	10 (55.6)	<0.001
	CC-1	44 (23.0)	3 (6.4)	16 (32.6)	10 (22.7)	1 (5.6)	7 (46.7)	7 (38.8)	
	CC-2/3	20 (10.4)	3 (6.4)	8 (18.3)	2 (4.5)	2 (11.1)	4 (26.6)	1 (5.6)	
Number of peritonectomies	0	11 (5.7)	4 (8.5)	3 (6.1)	1 (2.2)	3 (16.7)	0 (0.0)	0 (0.0)	0.001
	1–2	54 (28.2)	17 (36.1)	14 (28.2)	7 (15.9)	6 (33.3)	3 (20.0)	7 (38.8)	
	3–5	68 (35.6)	21 (44.6)	13 (26.5)	16 (36.3)	8 (44.4)	3 (20.0)	7 (38.8)	
	6–7	58 (30.3)	5 (10.6)	19 (38.7)	20 (45.4)	1 (5.6)	9 (60.0)	4 (22.1)	
Number of visceral resections	0	28 (14.6)	9 (19.1)	11 (22.4)	3 (6.8)	0 (0.0)	1 (6.7)	4 (22.1)	0.006
	1–3	108 (56.5)	34 (72.4)	21 (42.8)	23 (52.2)	10 (55.6)	11 (83.3)	9 (50.0)	
	>3	55 (28.7)	4 (8.5)	17 (34.6)	18 (40.9)	8 (44.4)	3 (20.0)	5 (27.7)	

Abbreviations: NACT-neoadjuvant chemotherapy; PM-peritoneal metastases; PCI- peritoneal cancer index; CC-Score – completeness of cytoreduction score.

Results

From July 2018 to Dec 2018, 191 patients were included in the study (Table 1). The primary tumor site was appendix in 49 (25.6%), colorectal (CRC) in 47 (24.6%), ovary in 44 (23.0%%), stomach in 18 (9.4%), mesothelioma in 15 (7.8%) and rare primary (or unusual indications for CRS; supplementary material 2) in 18 (9.4%). The median sPCI was 11 [range 0–39] and a CC-0/1 resection was obtained in 171 (89.4%). Neoadjuvant chemotherapy (NACT) was administered to 132 (69.1%) for PM.

Pathological findings

Median pPCI was 6 [range 0–39] (Table 2). The pPCI concurred with the sPCI in only 37 (19.2%) patients. Disease in normal peritoneum (surgical score 0) was seen in 39 (20.4%) patients. Lymph nodes were positive in 31.4% of which 20.9% were regN and 13.6% were perN. The nodes included those in relation to the resected bowel in 13 (6.8%), in the subperitoneal fat in 8 (4.1%), in relation to the omentum in 4 (2.0%) and paracardiac nodes in 3 (1.5%).

The primary tumor was resected for 94 patients (repeat resection in 28). The average number of regions dissected was 6.2 and sections per region was 7.2. Thus, on an average 45 blocks were prepared for each patient.

Ovarian cancer

Of the 44 patients with ovarian cancer, majority (88.6%) had high grade serous carcinoma. The median sPCI was 11 (range 0–27) (Table 3). The lower region was involved in 72.7% patients, middle in 61.3%, upper in 63.6% and small bowel region in 25.0% patients. No patient undergoing the first surgical intervention had disease in the upper and middle regions (excluding the omentum) without involvement of the lower region. Regional nodes were dissected in 77.2% and positive in 27.2%. Of these, 20.4% had involvement of pelvic nodes, 20.4% paraaortic and 20.4% had involvement perN.

Table 2
Pathological findings in 191 patients stratified according to primary tumor site.

Characteristic		All N = 191 (%)	Colorectal N = 47 (%)	Appendix N = 49 (%)	Ovary N = 44 (%)	Gastric N = 18 (%)	Mesothelioma N = 15 (%)	Rare primary N = 18 (%)	p-Value
Resection of the primary tumor	Performed	94 (49.2)	33 (70.2)	17 (34.6)	23 (52.2)	13 (72.2)	NA	8 (44.4)	<0.001
	Not performed	97 (50.1)	14 (29.8)	32 (65.4)	21(47.8)	5 (27.8)	NA	10 (55.6)	
Median pathological PCI		6 [0–39]	2 [0–23]	14 [0–39]	6 [0–26]	2 [0–15]	14 [4–35]	6 [0–26]	
Pathological PCI	0–9	114 (59.6)	39 (82.9)	19 (38.7)	26 (59.0)	15 (83.3)	1 (6.7)	14 (77.7)	<0.001
	10–19	46 (24.0)	4 (8.5)	11 (22.4)	16 (36.3)	3 (16.7)	10 (66.6)	2 (11.1)	
	20 or more	31 (16.2)	4 (8.5)	19 (34.6)	2 (4.5)	0	4 (26.6)	2 (11.1)	
Pathological PCI = surgical PCI	Yes	37 (19.2)	13 (27.6)	9 (18.3)	6 (13.6)	7 (38.8)	1 (6.7)	1 (5.6)	0.040
	No	154 (80.6)	34 (72.4)	40 (81.7)	38 (86.4)	11 (61.2)	14 (93.3)	17 (94.4)	
Number of blocks per region		7.16 +_5.22	7.87+_5.22	5.8 ± 5.96	6.8 ± 2.29	10.1 +_6.94	5.1 +_2.56	6.6 +_3.78	0.545
Regional nodes	Dissected	114 (59.6)	24 (51.0)	25 (51.0)	33 (75.0)	14 (77.7)	9 (60.0)	8 (44.4)	0.044
	Not dissected	77 (40.4)	23 (49.0)	24 (49.0)	11 (25.0)	4 (22.3)	6 (40.0)	10 (55.6)	
Positive nodes	Overall	60 (31.4)	17 (36.1)	11 (22.4)	12 (27.2)	11 (61.1)	6 (60.0)	3 (16.7)	0.324
	Related to primary	40 (20.9)	13 (27.6)	7 (14.2)	8 (18.1)	11 (61.2)	0 (0.0)	1 (5.6)	0.003
	Related to PM	26 (13.6)	5 (10.6)	4 (8.1)	9 (20.4)	0 (0.0)	6 (60.0)	2 (11.1)	0.179
Disease in normal peritoneum (surgical PCI = 0)	Present	39 (20.4)	11 (23.4)	6 (12.2)	12 (27.2)	3 (16.7)	4 (26.6)	3 (16.7)	0.510
	Absent	152 (79.6)	36 (76.6)	43 (87.8)	32 (72.8)	15 (83.3)	11 (83.4)	15 (83.3)	

Table 3
Clinical and pathological findings in patients with ovarian cancer, appendiceal tumors and colorectal cancer.

Characteristic		Ovarian cancer		Appendiceal tumors		Colorectal cancer	
		N = 44 (%)		N = 49 (%)		N = 47 (%)	
Timing of intervention	Primary CRS	7 (15.9)		NA		NA	
	Interval CRS	19 (43.1)					
	Secondary CRS	6 (13.6)					
	Salvage CRS	12 (27.2)					
Histology of peritoneal metastases	High grade serous	39 (88.6)		NA		NA	
	Low grade serous	1 (2.2)					
	Clear cell carcinoma	3 (6.8)					
	Endometroid adenocarcinoma	1 (2.2)					
Histology of peritoneal metastases	LGMCP	NA		22 (44.8)		NA	
	HGMCP			8 (16.3)			
	HGMCP-S			1 (2.0)			
	Mucinous adenocarcinoma			11 (22.4)			
	Non-mucinous adenocarcinoma			7 (14.2)			
Primary site for CRC	Colon	NA		NA		45 (95.7)	
	Rectum					2 (4.3)	
Timing of PM (CRC)	Synchronous	NA		NA		29 (61.7)	
	Metachronous					18 (38.3)	
Histology of peritoneal metastases	Adenocarcinoma	NA		NA		35 (74.4)	
	Mucinous adenocarcinoma					11 (23.4)	
	Signet ring cell carcinoma					1 (2.1)	
Involved region		Surgical	Pathology	Surgical	Pathological	Surgical	Pathological
	Upper region	26 (59.0)	28 (63.6)	16 (32.6)	15 (30.6)	15 (31.9)	13 (27.6)
	Middle region	26 (59.0)	27 (61.3)	17 (34.6)	12 (24.4)	16 (34.0)	22 (46.8)
	Lower region	27 (61.3)	32 (72.7)	17 (34.6)	13 (26.5)	25 (53.1)	24 (51.0)
	Small bowel regions	16 (36.3)	11 (25.0)	16 (32.6)	11 (22.4)	18 (38.2)	11 (23.4)
Regional lymph node dissection	Performed	34 (77.2)		25 (51.0)		24 (51.0)	
	Not performed	10 (22.3)		24 (49.0)		23 (49.0)	
Positive regional lymph nodes		12 (27.2)		11 (22.4)		17 (36.1)	
Site of nodal metastases	Primary tumor	0 (0.0)[b]		7 (14.2)		13 (27.6)	
	Pelvic	9 (20.4)		0 (0.0)		0 (0.0)	
	Para aortic	9 (20.4)		0 (0.0)		0 (0.0)	
	Omental	4 (9.0)		0 (0.0)		0 (0.0)	
	Involved bowel	7 (15.9)		1 (2.0)		4 (8.5)	
	Sub-peritoneal	1 (2.2)		3 (6.1)		1 (2.1)	
	Paracardiac	1 (2.2)		0 (0.0)		0 (0.0)	
Tumor in normal peritoneum adjacent to tumor nodules	Present	12 (27.2)		4 (8.1)		1 (2.1)	
	Absent	7 (15.9)		4 (8.1)		3 (6.3)	
	Not evaluated	25 (56.8)		42 (85.8)		43 (91.4)	
Tumor in surgical PCI 0 regions	Present	12 (27.2)		6 (12.2)		11 (23.4)	
	Absent	32 (72.8)		43 (87.8)		36 (76.6)	
Chemotherapy response[a] (Bohm score)	CRG-0	0 (0.0)		NA		NA	
	CRG-1	12 (27.2)					
	CRG-2	3 (6.8)					
	CRG-3	5 (11.3)					
Chemotherapy response (Japanese scoring system)	0	NA		NA		1 (2.1)	
	1					1 (2.1)	
	2					0 (0.0)	
	3					4 (8.1)	
Chemotherapy response (French scoring system)	Complete response	NA		NA		4 (8.1)	
	Major response					5 (10.6)	
	Poor response					6 (12.7)	

Abbreviations: CRS- cytoreductive surgery; NA-not applicable; LGMCP- low grade mucinous carcinoma peritonei; HGMCP- high grade mucinous carcinoma peritonei; HGMCP-S- high grade mucinous carcinoma peritonei with signet ring cells; CRC- colorectal cancer; CRG-chemotherapy response grade.
[a] The term 'chemotherapy response grade (CRG)' is used instead of chemotherapy response score.
[b] Included in pelvic and para aortic nodes.

The perN included omental nodes in 9.0%, nodes in the mesentery of resected bowel in 15.9%, nodes in the subperitoneal fat in 2.2% and paracardiac nodes in 2.2%. None of the patients had positive perN in absence of involvement of either pelvic or paraaortic nodes. In 6.8% patients paraaortic node involvement was present without pelvic node involvement. In 27.2% patients, involvement of normal looking peritoneum was established. In 43.2% patients, additional sections were taken adjacent to tumor nodules from the normal peritoneum and in 63.1% of these patients, microscopic disease was found in one or more evaluated regions. In 20 evaluated patients, none of the patients had a pathological complete response to chemotherapy.

Appendiceal tumors

The histological subtype of 49 patients with appendiceal tumors is provided in Table 3. Lymph nodes were positive in 11(22.4%) patients of which two had LGMCP. Metastatic nodes were regN in 14.2%, and perN in 8.1% (subperitoneal nodes in 6.1% and in the mesentery of resected bowel in 2.0%). Tumor in regions with a surgical PCI score of 0 was seen in 6 (12.2%) patients. In 8 (16.2%) patients, normal peritoneum adjacent to tumor deposits was evaluated and 50% had microscopic disease in it.

Colorectal cancer (CRC)

There were 45 patients with colonic primary tumors, 2 with rectal primary (Table 3). The upper region (regions 1, 2, 3) showed disease in 13 (27.6%) patients of which only 7 (14.8%) had involvement of the diaphragmatic peritoneum. In these the right was involved in 6 (12.7%), the left in 1 (2.1%) and both in 3 (6.3%) patients. 4/7 patients had a PCI of more than 20, 2 less than 10 and 1 more than 10.17 (36.1%)patients had positive lymph nodes, 13 (27.6%) regN and 5 (10.6%) had perN positive (subperitoneal -1 and bowel related -4). Pathological response to chemotherapy was evaluated for 21 patients of which 5 (23.8%) patients had a complete response, 6 (28.5%) patients had a good/major response and 10 (47.6%) had a poor response. Disease in regions with PCI score 0 was seen in 23.4% of the patients.

Discussion

Through this study we provide the background evidence for further evaluation of some potential pathological prognostic factors in patients undergoing cytoreductive surgery.

Pathological PCI and lymph node involvement: The surgical evaluation of disease extent was inaccurate in over 75%. The pPCI provides a more accurate and objective quantification of PCI. It should be computed in addition to the surgical PCI for all patients and its prognostic value determined in future studies. Currently, the prognostic value of lymph node involvement in relation to peritoneal disease (perN) is not known except for peritoneal mesothelioma in which it has a negative influence on survival [13]. There is a recommendation to remove perN in peritoneal mesothelioma but not for other primary tumors [13]. In ovarian cancer, 20% of the patients had positive perN, 8.1% with appendiceal tumors, 60% with peritoneal mesothelioma and 10.6% with CRC. Thus, nodal involvement in relation to peritoneal disease in not an uncommon finding. And it may be hypothesized that patients with perN have a worse prognosis than those without it. We recommended all resected specimens should be thoroughly evaluated for nodal disease; omental nodes should be evaluated in all patients. Bowel resections that are performed to address peritoneal disease should include regional lymphadenectomy as is performed for a primary tumor at that site [14].

Pathological response to chemotherapy: Chemotherapy response scores are used for colorectal, gastric and ovarian cancer [8,9,15]. It has been shown that a complete or near complete response is predictive of a longer survival, however, in poor and moderate responders, there is no recommendation regarding further chemotherapy-whether the same or a different regimen should be used. Secondly, the impact of multiple lines of chemotherapy on the chemotherapy response on pathology is not known. In our study, the use of such scores was not done for all patients at each centre. Collaborative studies should further establish the relevance of pathological response to chemotherapy. In 23.8% (5/21) patients with colorectal PM, a pathological complete response was found. It is probable, that patients who experience a very good response to systemic chemotherapy may derive little benefit from the addition of intraperitoneal chemotherapy [16].

Morphology of peritoneal deposits: Another significant finding in this study was disease in normal peritoneum adjacent to tumor nodules in more than 50% the evaluated patients in both mucinous appendiceal tumors and serous epithelial ovarian cancer. It has been proposed that complete removal of the parietal peritoneum should be performed for peritoneal mesothelioma, serous

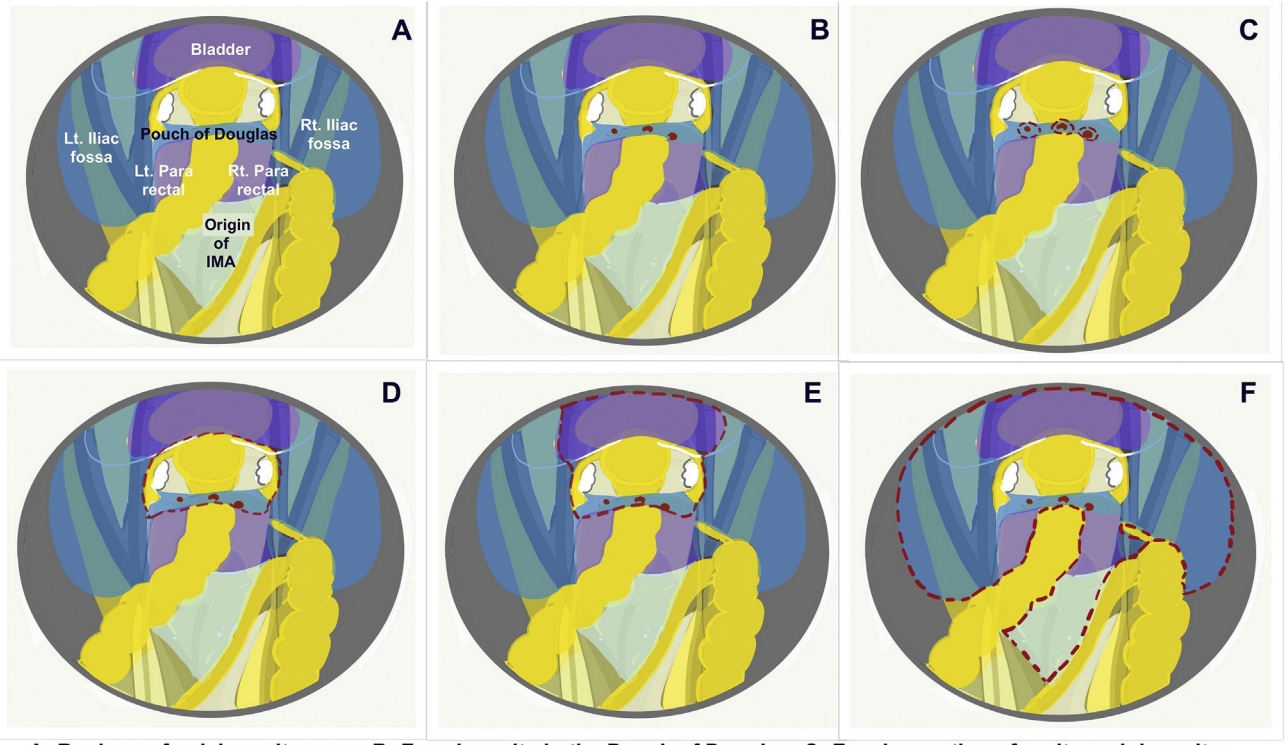

Fig. 1. This figure shows that variable extent of peritoneal resection can achieve a complete cytoreduction with same disease amount. Figures C–E show less to more extensive resection. (extent of resection is indicated by the red broken lines).

epithelial ovarian cancer and mucinous carcinoma peritonei of appendiceal origin as these represent peritoneal disease [17,18]. The peritoneal deposits secondary to these tumors are morphologically different from colorectal cancer and other tumors in which peritoneum in between tumor nodules seldom harbors microscopic disease. However, these findings are preliminary and need further confirmation. The basic information on morphological evolution of peritoneal metastases is missing in scientific literature. Further studies should look at this as it is important for determining the extent of peritoneal resection that is needed for each primary tumor type. Though peritonectomy procedures are defined anatomically, the extent of resection is defined by the size of residual disease. For a 1 cm deposit in the Pouch of Douglas, with no disease elsewhere in the pelvis, the extent of pelvic peritonectomy can vary from one surgeon to another-some may do a resection of the pouch of Douglas alone or region 6 or resect the entire peritoneum including that in the iliac fossae (Fig. 1). Whereas more extensive resection may not have much morbidity, resecting less peritoneum may be of consequence for some tumors like ovarian cancer where that normal peritoneum has a high probability of harboring microscopic disease. Contrary to this, for colorectal PM, less extensive resection may be sufficient as demonstrated by one retrospective study [19]. Perhaps, the peritoneum is the only site where the extent of surgical resection is defined by the size of residual disease and not anatomically. This study provides evidence for evaluating the role of more extensive surgery for serous epithelial ovarian cancer, mucinous appendiceal tumors and peritoneal mesothelioma.

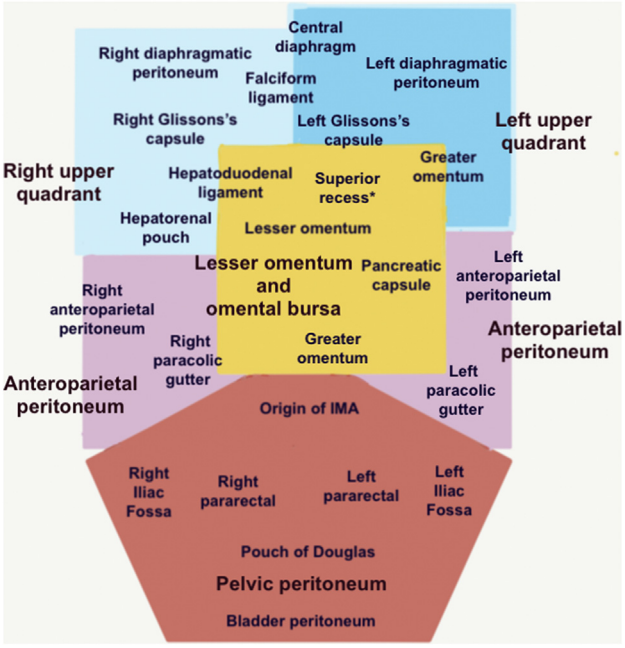

Fig. 2. Peritoneal regions included in the five peritonectomies described by Sugarbaker. *of the lesser sac

Regional distribution of peritoneal metastases

The extent of peritoneal disease has been quantified using various scoring systems, however, the disease distribution has not been considered [20–22]. Involvement of certain regions portends a poor prognosis even if a complete resection is possible e.g. involvement of the small bowel in colorectal PM [11]. One retrospective study has shown that involvement of the right upper quadrant peritoneum is associated with a poorer disease free and overall survival [23]. In this study, only 15/47 patients with CRC PM had surgery involving the upper regions. Of these only 7 patients had involvement of the diaphragmatic peritoneum on pathology and 4/7 had a PCI of more than 20 on pathology. We do not have the survival data, but this study shows that involvement of the subphrenic peritoneum in colorectal cancer is uncommon and is associated with a high PCI. Further evaluation of disease distribution can help prognostify and select patients for surgery. The other cancer where such knowledge can be of use is ovarian cancer [24].

With this study we also aimed to provide a broad outline for pathological evaluation of CRS specimens. We propose that all peritoneal regions resected should be evaluated for the presence or absence of disease and the PCI scored on pathology as well (Fig. 2). The size of the largest deposit in each region should be reported. Secondly, all potential sites of nodal disease like the bowel mesentery, subperitoneal fat and omenta should be thoroughly evaluated. Chemotherapy response should be evaluated for all patients.

A morphological description of the peritoneal disease in each region should be recorded by the surgeon and also provided to the pathologist. It will ensure that some changes that are difficult to identify after fixing the specimen like thickening and tiny nodules are not missed. Whereas such information may have no immediate

Pathological finding	**Increasing score** →			
PCI	0-9	10-19	20-29	30-39
Lymph nodes	Regional nodes negative , peritoneal nodes negative	Regional nodes positive, Peritoneal nodes negative		Regional nodes positive, Peritoneal nodes positive
Pathological response to chemotherapy	Complete response	Near complete response	Moderate response	Poor response
Regional distribution	Around the primary	Lower regions	Middle regions	Upper regions
Morphological presentation	No tumor in normal peritoneum adjacent to tumor nodules		Presence of tumor in the normal peritoneum adjacent to tumor nodules	

Fig. 3. Pathological variables that may have prognostic value and could be used to compute a scoring system to stage peritoneal metastases from different primary tumors.

impact on treatment, it will provide the vital missing information in scientific literature and make future evaluation and comparison of treatment outcomes more objective. A data set for reporting in provided in Supplementary material 3. The above parameters could in future used to compute a staging system for PM (Fig. 3). As with TNM staging, in which common parameters like the tumor stage and lymph node involvement correlate with prognosis across different tumor types, we hypothesize that the factors listed in Fig. 3 will have a bearing on the prognosis irrespective of the primary tumor site. This of course needs further prospective evaluation, development of a scoring system and its validation.

This study has limitations. All aspects of the protocol were not followed at all the centers. In addition, there is an inherent heterogeneity in the study due to the difference in the patient population and treatment protocols followed at each centre. Pathological response to chemotherapy was not evaluated for all patients. We have a short follow up and hence the survival outcomes are not available. However, performing the study prospectively gave us an opportunity to review the existing practices and minimize missing data.

Conclusions

The pathological extent of peritoneal spread differs from the surgical evaluation in majority of the patients. Lymph node involvement in relation to peritoneal deposits is common. Standardized methods of synoptic reporting of CRS specimens which include a description of the morphology, distribution, extent, nodal involvement and response to chemotherapy, could help capture vital prognostic information that may in future influence how these patients are treated.

Conflict of interests

The authors have no disclosures or conflict of interests

Funding

The authors received no funding for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.019.

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