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TOPIC HIGHLIGHT

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Cytoreductive surgery in primary advanced epithelial ovarian cancer

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Abstract

Epithelial ovarian cancer is one of the most common malignancy and one of the principal causes of death among gynaecological neoplasm. The majority of patients (about 70%) present with an advanced International Federation of Gynaecology and Obstetrics stage disease. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy (CT). An increasing proportion of patients undergoing complete cytoreduction to no gross residual disease (RD) is associated with progressively longer overall survival. As a counterpart, some authors hypothesized the improving in survival could be due more to a less diffused initial disease than to an increase in surgical cytoreduction rate. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove. Adjuvant and hyperthermic intraperitoneal CT could play a decisive role in the coming years as the completeness of macroscopic disease removal increases with advances in surgical techniques and technology. The introduction of neo-adjuvant CT moreover will play a decisive role in the next years Anyway cytoreduction with no macroscopic residual of disease should always be attempted. However the definition of RD is not universal. A unique and definitive definition is needed.

Key words: Ovarian cancer; Cytoreduction; Complete; Hyperthermic intraperitoneal chemotherapy

Core tip: The present paper reviews the efficacy of complete cytoreductive surgery in the treatment of primary advanced epithelial ovarian cancer. Outlining the importance for standard criteria in defining the completeness of cytoreduction. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove. Adjuvant and hyperthermic intraperitoneal chemotherapy could play a decisive role in the coming years as the completeness of macroscopic disease removal increases with advances in surgical techniques and technology.

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INTRODUCTION

Approximately 225500 women worldwide are diagnosed

each year with ovarian cancer. About 140200 women die every year for this disease[1]. In the United States, ovarian cancer remains the leading cause of death among women diagnosed with gynaecological cancer[2]. The strongest predictor of mortality has been demonstrated to be the International Federation of Gynaecology and Obstetrics stage. Unfortunately the majority of patients have an advanced-stage of disease at the time of diagnosis. This is strongly linked with the poor prognosis of the disease[3,4]. Moreover most of the patients with advanced-stage disease will experience relapse. Even with a good response to primary treatment, only 20%-25% of women can be expected to be long-term survivors[5]. Survival rates are strongly influenced by the adjuvant chemotherapy (CT) regimen. However, primary cytoreductive surgery (CRS) to minimize the amount of residual disease (RD) is equally important. The fist description of a survival advantage associated with an ovarian tumor debulking procedure was published by Meigs in 1934[6]. A few decades after, the necessity of initial CRS in treatment of epithelial ovarian cancer (EOC) gained traction with the report by Griffiths[7]. Hoskins *et al*[8,9] reported two studies of the Gynaecologic Oncology Group (GOG) (protocols 52 and 97), that illustrated the key points of CRS for advanced-stage EOC: (1) the inverse relation between the maximal diameter of RD and overall survival (OS); (2) the maximal diameter of RD above which CRS has no appreciable effect on survival; and (3) introduced the concept of multi-factoriality of survival determinants. During the last 20 years, the improvements in surgical capability have facilitated the achievement of maximal cytoreduction in an increasingly higher percentage of patients with as consequence related decrease of the average of RD maximal diameters[9-20]. Similar advances in CT agents and regional delivery regimens have magnified the potential survival advantage associated with a maximal surgical effort[7].

PRIMARY CRS

Treatment of advanced EOC has advanced in last 10 years. The innovation of the last three decades in the surgical management of peritoneal cancer diffusion introduced the possibility to treat patients that were long considered untreatable. Peritoneal carcinomatosis had been considered as a metastatic inoperable grade of cancer, before the Sugarbaker era. Actually, the universally accepted treatment diagram for advanced EOC considers as key points the maximal CRS and the adjuvant CT also for grossly peritoneal diffused disease. Grade ⅢC and Ⅳ are no longer considered as "lost". Many studies have demonstrated that a progressively more aggressive surgical effort is associated with improvements in disease-free and OS rates. It has been demonstrated the necessity to perform aggressive surgery in dedicated centres with high volume surgeons. High volume surgeons have, in fact, demonstrated to have an in-hospital mortality lower up to 69% than low volume surgeons[21]. The concept of "population-based cytoreduction", introduced in a meta-analysis in 2002, stimulated reflection about the necessity to aggressively treat each single case of advanced EOC to gain in survival for the whole considered population[22]. The more the surgeon became radical and increased his/her surgical volume the more he/she prolongs the disease-free and OS and reduces the in-hospital mortality. As a counterpart, some authors hypothesized the improving in survival could be due more to a less diffused initial disease than to an increase in surgical cytoreduction rate[23-25]. Moreover the biology of the tumor plays an important role in survival benefit of surgery. It's still undefined how the intrinsic features of the tumor make intra-abdominal implants easier to remove[26]. In general, upper abdominal tumor implants are suggestive of an aggressive tumor biology[6]. Covens and Berman criticized the role of CRS in advanced EOC. They proposed that both survival and surgical resectability are mostly determined by tumor biology instead of the operative effort by the surgeon[24,27]. The retrospective review of data from the Scottish Randomized Trial in Ovarian Cancer revealed in a population of 889 patients with disease stage ranging from IC to IV that the benefit of optimal debulking surgery seems to depend from the extent of disease before surgery[25]. The trial stratified patients into four pre-operative prognostic group depending on the staging. Survival was then analysed on the basis of the extent of CRS by stratification into three groups: No gross RD, RD $\leqslant$ 2 cm, RD $\geqslant$ 2 cm. Patients in the first two groups with a less extensive pre-operative disease benefited from CRS to RD $\leqslant$ 2 cm. Patients in the other two groups did not increase the survival with a CRS to RD $\leqslant$ 2 cm. Authors proposed to consider the tumor biology as determinant in survival and that CRS could not completely supply to the poor prognosis given by the intrinsic aggressiveness of some species of cell-clones.

The staging procedure could be performed by laparoscopy or *via* a vertical incision. An open staging procedure is the most trustworthy in order to assess the extent of disease and to evaluate the possibility to proceed with a complete cytoreductive procedure. All intra-abdominal surfaces and organs should be palpated, including the diaphragm, liver, spleen, gall bladder, small and large intestine, and mesentery. It's important to carefully evaluate the retroperitoneum for bulky adenopathy. Samples of the diffused cancer should be obtained, usually from involved omentum or adnexa. In the absence of gross extra-ovarian disease, multiple peritoneal biopsies should be obtained, along with a pelvic and para-aortic lymphadenectomy. In patients with early-stage ovarian cancer during the CRS phase, systematic lymphadenectomy should be part of the complete staging procedure. Maggioni *et al*[28] demonstrated as nearly 25% of patients with apparent early-stage ovarian cancer who undergo lymphadenectomy are upstaged to stage ⅢC due to the presence of node metastases. Some authors consider the role and benefit of systematic lymphadenectomy as unclear in patients with advanced-stage EOC. Panici *et al*[29]

randomized 427 patients with stage Ⅲ/Ⅳ EOC to either systemic lymphadenectomy or resection of bulky nodes. The 5-year OS rate was of 48.5% and 47%, respectively with no statistical significance differences. However they reported a longer progression-free survival in the systemic lymphadenectomy group (31.2%), than in the no-lymphadenectomy group (21.6%). Parazzini *et al*[30] analysing 456 women with advanced stage Ⅲ/Ⅳ ovarian cancer, demonstrated no correlation between nodal status and survival. Moreover in advanced EOC nodal status was not a prognostic factor for patients undergone to optimal cytoreduction.

Complete cytoreduction is reached when no visible tumor remains after the surgical procedure. Confusion exists in defining the results of the surgical intervention in terms of RD. The term "optimal" cytoreduction has been variably defined during the years in the different studies ranging from 0 to 2 cm in RD diameter. The GOG defined optimal the remaining of residual nodules of 1 cm or less[31]. Alternatively as optimal has been given the definition of no RD[31-35]. No residual tumor has also been described as complete cytoreduction[10,34]. A survey among members of the society of Gynaecologic Oncologists has been conducted. Results from this study demonstrated the heterogeneity of believing. About 12% of respondents defined no RD as optimal cytoreduction and 60.8% used the threshold of 1 cm to define the same concept[36]. Actually however the most largely adopted is the GOG classification which defines as optimal the RD of ≤ 1 cm.

Starting from this classification a number of prospective and retrospective studies have been conducted to investigate the feasibility of and the impact on survival of CRS in advanced EOC.

Generally CRS for EOC can be divided into simple and radical surgical procedures. Simple CRS consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, limited excision of pelvic/para-aortic lymph nodes, peritoneal excision, and sometimes segmental bowel resection. These procedures can be performed in the majority of patients with low risk of complications. To achieve optimal cytoreduction, surgery for advanced EOC frequently requires the addition of radical procedures: radical oophorectomy, rectosigmoid colectomy, multiple bowel resections, diaphragm peritonectomy or resection, liver resection, porta hepatis surgery, splenectomy, distal pancreatectomy, gastric resection, extensive nodal debulking, and intrathoracic surgery, These procedure could accomplish an higher rate of complications[7,37-68].

Since the first reports about the feasibility and the efficacy of optimal CRS in advanced EOC many authors have published about the topic. Many of them, however, reported case series in which patients have not homogeneously undergone CT or presented data without survival analysis focusing on the impact of RD. The more recent reports reach a major homogeneity from the chemotherapeutic point of view and have evaluated more extensively the impact and the extension of CRS and the RD.

Up to now, 15 studies have been published. The majority of them report cases treated with the standard systemic treatment of combined platinum-taxanes CT and CRS. Only one analyzed cases treated also with intraperitoneal CT[69]. Published studies divide patients into different classes of cytoreduction. The most utilized is the three level divisions: RD 0, 0-1, > 1 cm. In few studies a subgroup division is adopted. Some authors preferred to divide patients either into RD 0, 0-0.5, 0.6-1, 1-2 and > 2 cm or into RD 0, 0-1, 1-2, > 2 cm. Lastly, one paper divides patients into RD 0, 0-1, 1-5 and > 5 cm (Table 1).

This division demonstrated as no univocal evaluation of RD has been still adopted. Eisenkop *et al*[12] in 2003 reported a retrospective series of 408 patients with ⅢC stage EOC treated with either cisplatin/ciclophosfamide or paclitaxel/carboplatin CT and CRS. They reported an OS in the RD 0 group of 76.2 mo decreasing to 28.6 in the RD > 1. In the same year, Ozols *et al*[70] published a prospective analysis of 792 stage Ⅲ patients with a paclitaxel+cis-/carboplatin CT regimen divided into RD 0 and RD 0-1 which demonstrated an OS for the first group > 60 mo. OS reduced to 44 mo in the second group. In 2006 three papers have been published reporting stage Ⅲ-ⅢC patients. Two retrospective studies from Chi *et al*[13] and Aletti *et al*[14] reported both series of patients treated with either cisplatin/ciclophosphamide or paclitaxel/cisplatin CT added to CRS. Chi *et al*[13] divided patients into subgroups which distributed the RD into subcentimeters families reporting an OS of 106 mo for the RD 0 group progressively decreasing to 34 mo for the RD > 2 cm. Aletti reported an OS > 84 mo for the RD 0 and of 16 mo for RD > 2 cm. The last 2006 publication is the prospective report from Armstrong *et al*[69]. They reported a series of 415 women treated with cisplatin/paclitaxel CT administered either intraperitoneally or intravenously. For the two CT route (intraperitoneal and intravenous) groups they reported similar OS for RD 0 cm and RD 0-1 cm (78/75 mo and 127/135 mo respectively). Winter *et al*[15] and Wimberger *et al*[71] published another two retrospective reports. The first one reported about 861 patients with ⅡB-Ⅳ stage EOC which undergone paclitaxel/cisplatin or ciclophosphamide/cisplatin CT and CRS, with OS for RD 0 group of > 84 mo. The second one analyzed a series of 1895 stage Ⅳ women with carbo-/cisplatin + paclitaxel CT with OS ranging from 71.9 to 35 mo for RD 0 cm and RD > 1 cm groups respectively. Salani *et al*[72] also reported their retrospective series of 125 stage Ⅲ-Ⅳ patients tretated with cis-/carboplatin+palcitaxel CT with an OS ranging from 46.4 to 12 mo in RD 0 cm and RD > 1 cm respectively. The 2008 report by Winter *et al*[15] collected 360 women with stage Ⅳ EOC treated with carbo-/cisplatin+paclitaxel CT and CRS. They divided patients into groups ranging from RD 0 cm to RD > 5 cm. The OS ranges from 64.1 to 20.4 mo in the first and in the last group respectively. du Bois *et al*[17] and Bookman *et al*[73] published the two largest series of 3123 and 4312 patients respectively. du Bois *et al*[17] collected retrospectively patients with stage ⅡB-Ⅳ EOC who underwent carbo-/cisplatin+paclitaxel

Table 1 Cahracteristics of the included studies

Ref.	*n*	Disease stage (FIGO)	Age (yr)	Residual disease (cm)	*n* (%)	Overall survival (mo)	Associated cht	Route
Eisenkop *et al*[12]	408	ⅢC	63	0	351 (86)	76.2	PC, TP	*iv*
				0-1	41 (10)	32.2		
				> 1	16 (4)	28.6		
Chi *et al*[13]	465	ⅢC	60	0	67 (15)	106	NA	*iv*
				0-0.5	70 (15)	66		
				0.6-1	99 (21)	48		
				1-2	53 (11)	33		
				> 2	176 (38)	34		
Aletti *et al*[14]	194	ⅢC	64	0	46 (24)	> 84	PC, TP	*iv*
				0-1	85 (44)	34		
				1-2	22 (11)	25		
				> 2	41 (21)	16		
Winter *et al*[15]	1895	Ⅲ	57	0	437 (23)	71.9	TP, TC	*iv*
				0-1	791 (42)	42.4		
				> 1	667 (35)	35		
Winter *et al*[16]	360	Ⅳ	59	0	29 (8)	64.1	TP, TC	*iv*
				0-1	78 (21)	28.7		
				1-5	164 (46)	29.8		
				> 5	89 (25)	20.4		
du Bois *et al*[17]	814 (26)	ⅡB-ⅢB	59	0	1046 (34)	99.1	TP, TC, TC-TOP, TCE	*iv*
	1779 (57)	ⅢC		0-1	975 (31)	36.2		
	530 (17)	Ⅳ		> 1	1105 (35)	29.6		
Peiretti *et al*[18]	199 (76)	ⅢC	58	0	115 (44)	> 61.3	NA	NA
	60 (24)	Ⅳ		0-0.5	50 (19)	61.3		
				0.6-1	33 (13)	42.4		
				1-2	18 (7)	35.3		
				2	43 (17)	42.6		
Wimberger *et al*[19]	213 (28)	ⅡB-ⅢB	NA	0	227 (30)	> 84	PC, TP	*iv*
	548 (72)	ⅢC-Ⅳ		> 1	247 (32)	37		
					287 (38)	31		
Armstrong *et al*[69]	415	Ⅲ	56	0 (*ip* cht)	78 (38)	NA	TP	*iv*, *ip*
				0-1 (*ip*)	127 (72)	53		
				0 (*iv* cht)	75 (36)	78		
				0-1 (*iv*)	135 (64)	39		
Ozols *et al*[70]	792	Ⅲ	56	0	281 (35)	> 60	TP, TC	*iv*
				0-1	511 (65)	44		
Wimberger *et al*[71]	573	Ⅳ	59	0	70 (12)	54.6	TP, TC	*iv*
				0-1	168 (29)	25.8		
				> 1	334 (58)	23.9		
Salani *et al*[72]	97 (78)	Ⅲ	63	0	39 (31)	46.5	PC, TP	*iv*
	28 (22)	Ⅳ		> 1	53 (42)	28.3-37.8		
					23 (18)	12		
Bookman *et al*[73]	3681 (85)	Ⅲ	59	0	1044 (24)	68	TC	*iv*
	631 (15)	Ⅳ		0-1	1949 (45)	40		
				> 1	1319 (31)	33		
Chang *et al*[74]	189 (93.1)	ⅢC	54	0	63 (31)	86	TP, TC	*iv*
	14 (6.9)	Ⅳ		0-1	77 (37.9)	46		
				> 1	63 (31)	37		

PC: Platinum-cyclophosphamide; TP: Paclitaxel-cisplatin; TC: Paclitaxel-carboplatin; TC-TOP: TC-topotecan; TCE: TC-epirubicine; cht: Chemoterapy; NA: Not declared/assessed; FIGO: The International Federation of Gynecology and Obstetrics.

CT for stage ⅡB-ⅢB and carboplatin/paclitaxel and topotecan or epirubicin for more advanced stages. He reported an OS of 99.1 mo for RD 0 group decreasing to 29.6 mo for RD > 1 cm. Bookman *et al*[73] reported 4312 women with stage Ⅲ-Ⅳ disease undergone to carboplatin/paclitaxel and topotecan or epirubicine CT regimen with an OS of 68 mo for RD 0 cm and 33 mo for RD > 1 cm.

In 2010 three retrospective papers were published mixing stage ⅢB-Ⅳ patients. Peiretti *et al*[18] described 259 patients without publishing the intravenous CT regimen he reported an OS of > 61.3 mo for RD 0 and 41.6 for RD > 2 group. Interesting data in this paper regards the peculiar distribution of the OS among the RD groups. The authors divided patients into RD 0, RD 0.1-0.5 cm, RD 0.6-1 cm, RD 1-2 cm and RD > 2 cm. RD 0 cm and RD 0.1-0.5 cm have the same OS, RD 0-1 cm and RD > 2 cm patients have similar OS contrastingly with

the OS of RD 1-2 cm group who have a 10 mo shorter OS. These data contrast with all the other studies where the OS progressively declined with the increasing of the amount of RD. Kommoss *et al*[20] described 287 without the intravenous CT regimen with ⅢB-Ⅳ stage disease. RD 0 cm group reached an OS of 68.8 mo and the RD > 1 cm of 18.2 mo. In 2010, Wimberger *et al*[19] published another retrospective trial of 573 women with stage Ⅳ disease treated with carbo-/cisplatin and paclitaxel intravenous CT with an OS of 54.6 mo for RD 0 cm and 23.9 mo for RD > 1 cm group. The last paper about the effect of CRS in advanced EOC has been published in 2012 by Chang *et al*[74]. This retrospective description of 224 cases of stage ⅢC-Ⅳ patients with adjuvant platinum-paclitaxel CT with an OS of 86 mo in RD 0 cm and of 37 in RD > 1 cm group.

All the described papers demonstrated that CRS plays a pivotal role in advanced EOC treatment. The necessity of adjuvant CT has already been demonstrated and the necessity to reach a progressively more radical surgical cytoreduction has not been contradicted in the last 30 years. Surgical effort must be absolute. The extent of cytoreduction should be extended as much as is possible. The majority of reported studies adjust data for many differently combined factors such as: ASA, performance status, ascites, histology, tumor grade, RD, operative time, diaphragm or mesentery involvement, disease site in general. Even after these adjustments, data demonstrated always the same: as more the CRS is radical as more the OS is longer. The only exception to this rule derived from the study by Peiretti *et al*[18] in which OS rate doesn't linearly correlate to the RD group. The correspondence between the increasing of RD and the diminishing of OS seen in all the published literature in Peiretti's paper found a partial confirm.

The existing literature shows as the percentage of RD 0 procedures is absolutely different between the different centers and it doesn't apparently depend from the number of the treated patients. The number of enrolled patients in the published studies in fact could, in our opinion, be considered as a proxy of the surgical activity of the centers. In fact all the studies but three are retrospective and the evaluated periods of time are all comparable. The reported series have been all described slightly different CT regimens. Except for the Armstrong *et al*[69] study all the patients received intravenous CT. Observing the percentage of RD 0 reaching it seems to not be related to the CT regimen. The same could be observed for OS. Lastly, since the first publication about the discussed topic (2003) and the last (2012), there have not been major changes in the outcome of the treatment of advanced EOC by CRS and CT. As stated before, this suggests the presence of other factors from which depend the survival outcomes. Recent studies demonstrated the possibility to apply to ovarian cancer different drugs respect to the standard platinum based CT as bevacizumab[75]. However it has to be validated on the long course. Lastly different studies have investigated the possibility to apply weekly platinum/taxanes based CT regimens[76].

One topic that has not been largely investigated by the different authors is the quality of life (QoL) in the treated patients. It is a neglected area that should be more considered as a substantial part of the treatment of these women. Maximizing the surgical effort to eradicate the disease necessarily conduces to more aggressive procedures with the possibility to increase the morbidity. The evaluation of the impact of such a kind of procedures on the QoL of patients will necessarily lead to exaltation of the benefits of the neo-adjuvant therapies which could potentially reduce the disease load and consequently the surgical aggressiveness. Moreover the evaluation of the QoL must be pivotal in treating patients with advanced EOC in situations where the 5-year survival rate and so on the complete heal is not so relevant as the disease free survival and the quality of the gained surviving period. Introduction of neo-adjuvant CT regimen and the progressively more diffused use of hyperthermic intraperitoneal CT will play a decisive role in the next years in reaching a progressively more frequent removal of all macroscopic RD. They will also contribute to discern those factors other than CRS aggressiveness which strongly influence the survival outcomes.

CONCLUSION

Authors are used to report differently the results of CRS procedures, univocal definition of CRS results is needed. In order to increase the OS complete cytoreduction (RD 0 cm) should be always attempted and the primary aim of CRS should be no macroscopic RD.

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