Ann Surg Oncol (2016) 23:2515–2521
DOI 10.1245/s10434-015-5069-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Surgical Complexity Impact on Survival After Complete Cytoreductive Surgery for Advanced Ovarian Cancer

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ABSTRACT

Introduction. The direct relationship between surgical radicality to compensate biologic behavior and improvement of patient outcome at the time of primary or interval cytoreduction remains unclear.

Objective. The aim of this study was to evaluate the impact of disease extension and surgical complexity on survival after complete macroscopic resection for stage IIIC–IV ovarian cancer.

Materials and Methods. Medical records from seven referral centers in France were reviewed to identify all patients who had complete cytoreductive surgery for stage IIIC–IV epithelial ovarian, fallopian, or primary peritoneal cancer. All patients had at least six cycles of carboplatin and paclitaxel combination therapy.

Results. From the 374 consecutive patients with complete cytoreduction who were included in this study, stage, grade, upper abdominal disease, surgical complexity, and carcinomatosis extent were significantly associated with disease-free survival (DFS) at univariate analysis. Stage IV and the need for ultra-radical procedures were significantly associated with lower overall survival (OS). On multivariate analysis, radical surgery, including more than two visceral resections, was significantly associated with decreased DFS and OS.

Conclusions. Patients who need complex surgical procedures involving two or more visceral resections in order to achieve successful complete cytoreduction have worse outcome than patients with less extensive procedures. The negative impact of surgical complexity was not significant in patients who underwent upfront procedures. Tumor volume and extension were associated with decreased DFS in patients undergoing a primary surgical approach. This adds to the evidence that, even though complete cytoreduction is currently the objective of surgery, tumor load remains an independent poor prognostic factor and probably reflects a more aggressive behavior.

Complete removal of all macroscopic tumor is the single most important prognostic factor for long-term survival in patients with advanced ovarian cancer.[1,2] Peroperative care, infrastructure, and resectability criteria have evolved. Surgical skills, especially the approach to advanced ovarian cancer involving the upper abdomen, have improved the rate of optimal cytoreduction,[3] and the addition of these procedures has increased the rate of complete cytoreduction surgery. On the other hand, the outcome of surgery also depends on the patient's ability to tolerate an extensive surgical approach.[4] Morbidity and mortality associated with these procedures are strongly related to the performance of extended abdominal visceral resections.[5]

First Received: 18 September 2015;
Published Online: 23 March 2016

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Literature evidence shows that completeness of cytoreduction (CC) has a more significant influence on survival than the extent of peritoneal disease. Memorial Sloan Kettering Cancer Center (MSKCC) experience demonstrated that complete cytoreduction decreases the risk of recurrence and death irrespective of the initial presence and volume of upper abdominal tumor burden present at the beginning of surgery.[4] Most authors have focused on the importance of complete cytoreduction and the effect of surgical outcome criteria on survival, especially since upper abdominal procedures have been incorporated in order to ensure no macroscopic residual disease is present.

The primary aim of this study was to evaluate the impact of disease extension and surgical complexity on survival in stage IIIC–IV patients with complete macroscopic resection after primary or interval debulking surgery for advanced ovarian cancer.

MATERIALS AND METHODS

A search of the institutional patient database was performed to retrospectively identify all patients who underwent cytoreductive surgery (CRS) for stage IIIC–IV epithelial ovarian, fallopian, or primary peritoneal cancer between January 2003 and December 2007 in seven institutions in France that were recognized as referral centers in the treatment of ovarian cancer. In all cases, preoperative imaging included a computed tomography (CT) of the chest, abdomen, and pelvis, and, in selected cases, a positron emission tomography (PET) CT.

All operations were performed by a gynecologist oncologist under the supervision of a senior gynecologist oncologist. All patients underwent complete cytoreduction surgery to no macroscopic residue, and had at least six cycles of carboplatin and paclitaxel combination therapy. Adjuvant chemotherapy was administered within 2 months of surgery, when feasible, at the discretion of the treating oncologist. No anti-angiogenic agents were used in any patient included in the current study. Patients in whom surgical procedures were not detailed enough in the operative records, and patients with non-epithelial histology or borderline tumors were excluded from the study. The study was approved by the Institutional Review Board from the Institut Claudius Regaud (ICR).

Medical records were reviewed and patient demographic data, with particular emphasis on operative records to detail the extent and distribution of disease spread, surgical procedures, chemotherapy treatment, and follow-up data, were included. Extent and distribution of the 13 abdominopelvic regions and surgical outcome was evaluated using the peritoneal cancer index (PCI) and CC score.[6] Surgical complexity was defined according to visceral resections, and supraradical procedures were defined as cytoreduction surgeries requiring at least two visceral resections. Surgical and pathology variables were analyzed to investigate their potential as biological markers of poor outcome in patients who underwent a complete surgical procedure.

Statistical Methodology

Data were summarized using frequency and percentage for categorical variables, and median and range for continuous variables. All reported p values were two-sided. For all statistical tests, differences were considered significant at the 5 % level, and statistical analyses were performed using STATA 12.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 374 consecutive patients with complete CRS type CC0 were included in the study. Median age was 58 years at diagnosis (24–85 years), and 325 patients (86.9 %) were stage IIIc and 49 (13.1 %) were stage IV. Patient and tumor characteristics are shown in Table 1. Overall, 125 patients (33.4 %) underwent primary CRS, 194 patients (51.9 %) underwent interval cytoreduction surgery after three to four cycles of neoadjuvant chemotherapy, and 55 patients (14.7 %) underwent surgery after six cycles of neoadjuvant chemotherapy. Twenty-one patients (5.7 %) had a hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, and 26 patients (7.2 %) had intraperitoneal chemotherapy. Median PCI was 8 (range 0–31) for all patients included in the study, 11 (range 3–31) for patients who underwent upfront surgery, 6 (0–31) for patients who underwent interval surgery after three to four cycles of chemotherapy, and 7 (0–17) for patients who underwent surgery after six cycles of chemotherapy. Para-aortic lymphadenectomy was performed in 310 patients (83.6 %), while 185 patients (49.5 %) required at least one visceral resection. Large bowel resection was required in 40 % of patients, small bowel resection in 10 % of patients, and multiple bowel resections in 12 % of patients. Upper abdominal procedures consisted of right diaphragmatic procedures in 42.5 % of patients, left diaphragmatic procedures in 14.2 % of patients, liver resections in 4 % of patients, splenectomies in 10 % of patients, and procedures including peritoneal stripping of the porta hepatis and/or celiac lymph node resection in 2.4 % of patients (Fig. 1).

After a median follow-up of 47.7 months [95 % confidence interval (CI) 44.2–52.4], median progression-free survival (PFS) was 19.5 months (95 % CI 18–21.8), with an estimated disease-free survival (DFS) of 77.9 % (95 %

TABLE 1 Clinical characteristics

	N (%)
Stage	
IIIC	325 (86.9)
IV	49 (13.1)
Grade[a]	
1	27 (9.2)
2	89 (30.3)
3	178 (60.5)
Histologic type	
Serous	274 (73.2)
Clear cell	10 (2.7)
Mucinous	9 (2.4)
Endometrioid	36 (9.6)
Other[b]	45 (12)
Surgical procedures	
Hysterectomy	348 (93)
BSO	358 (96)
Omentectomy	367 (98.1)
Bowel resection	
Small bowel resection	36 (9.7)
Large bowel resection	149 (39.9)
Multiple bowel resections	45 (12.1)
Appendectomy	250 (67)
Lymphadenectomy	
Pelvic	319 (85.5)
Aortic	310 (83.6)
Peritonectomy	
Right upper quadrant	159 (42.5)
Left upper quadrant	53 (14.2)
Median preoperative CA 125	800 (18–90,000)
Median ascites, ml (range)	50 (0–8000)

BSO bilateral salpingo-oophorectomy

[a] Unknown for 80 patients

[b] Undifferentiated, transitional, mixed

CI 73.3–81.8) at 12 months, 40 % (95 % CI 34.9–45) at 24 months, 26.7 % (95 % CI 22.1–31) at 36 months, and 22.2 % (95 % CI 17.9–26.9) at 48 months. Median DFS was 24.2 months in patients undergoing primary surgery, 19.1 months in patients undergoing interval procedures, and 16.9 months in patients undergoing surgery after six cycles of chemotherapy. Median overall survival (OS) was not reached. Estimated OS was 96.7 % (95 % CI 94.3–98.1) at 12 months, 86.2 % (95 % CI 82.1–89.4) at 24 months, 73.2 % (95 % CI 68–77.7) at 36 months, and 61.1 % (95 % CI 55–66.5) at 48 months.

On univariate analysis, stage, grade, upper abdominal disease, surgical complexity, neoadjuvant chemotherapy, and PCI were significantly associated with DFS, while stage and surgical complexity were significantly associated with OS. PCI remained a prognostic factor with a trend towards decreased OS (see Table 2). On multivariate analysis, decreased PFS was found in patients who underwent interval cytoreduction and patients who required two or more visceral resections. Surgical complexity was also significantly associated with decreased OS.

In the subgroup of patients who underwent upfront surgery, stage, grade, and carcinomatosis extent were significantly associated with decreased PFS in univariate analysis. Grade was the only factor significantly associated with decreased OS, and surgical complexity was not significantly associated with decreased PFS ($p = 0.08$). In multivariate analyses, disease extension measured by the PCI was the only significant factor associated with decreased PFS, with a non-significant trend to decreased OS ($p = 0.07$). Resistance to platinum after complete cytoreduction was significantly associated with high grade, papillary serous histology, upper abdominal disease, higher tumor load, and surgical complexity. No specific locations were associated with decreased survival, with the exception of bowel spread. A significant association was noted between increased progression during the 6 months that followed the end of chemotherapy and bowel disease requiring at least one bowel resection. There was also a non-significant association between patients who required celiac lymph node resection and resistance to platinum ($p = 0.09$).

DISCUSSION

As the absence of visible tumor residue is the most important prognostic factor for long-term survival,[1] it is hypothesized that this effect is driven by the removal of chemoresistant clones and poorly vascularized tumor; a higher growth fraction in better perfused, small residual tumors increases chemosensitivity and improves host immunocompetence by resection of bulky tumor.[7] Most of the previous reports focus on the survival effect of residual disease and timing of surgical effort in patients with extended disease requiring complex procedures; however, the effect of disease burden as well as surgical aggressivity have been poorly investigated.

The extent of disease as a marker of biological aggressiveness in patients with no residual tumor after surgery remains under discussion. Eisenkop et al. demonstrated that complete surgical cytoreduction has a more significant independent influence on survival than total extent of intra-abdominal tumor burden.[8] They also found that there are no specific intra-abdominal tumor locations or surgical procedures that correlate with tumor-inherent biological aggressiveness.[8] In our series, two or more bowel resections were associated with early recurrent disease. These

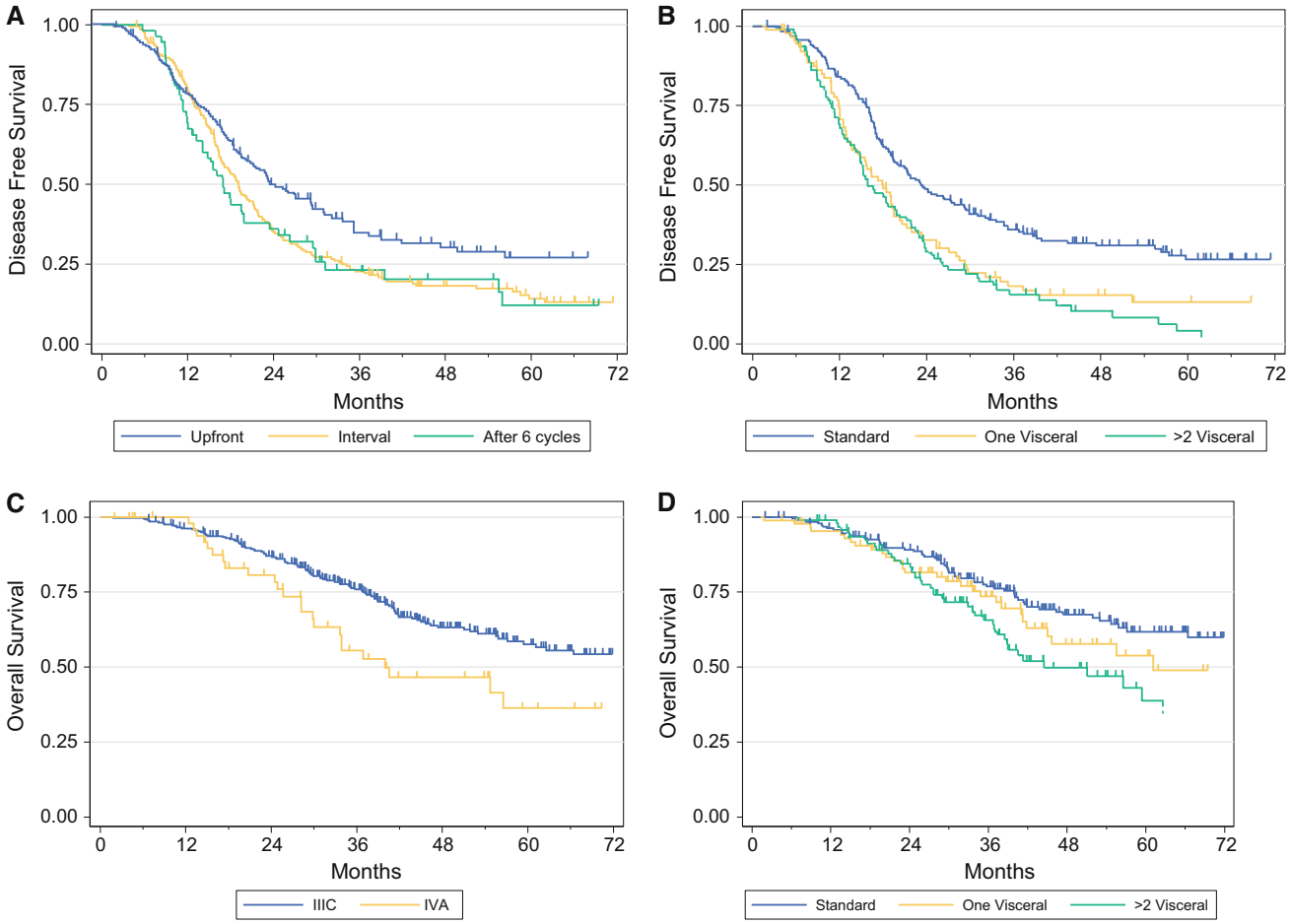

FIG. 1 Disease-free and overall survival. **a** DFS in patients with primary, interval surgery after three to four cycles, and surgery after six cycles of neoadjuvant chemotherapy; **b** DFS according to surgical complexity; **c** OS in patients with stage IIIC and IV; **d** OS according to surgical complexity. *DFS* disease-free survival, *OS* overall survival

patients presented with higher tumor burden, with a median PCI of 16 (2–31), compared with a median PCI of 7 (0–31) ($p < 0.001$) in patients with no bowel resection. No significative difference was observed between the number of bowel resections and time of surgery, with 20 patients (44.4 %) opting for an upfront surgical approach, 21 patients (46.7 %) opting for interval surgery, and 4 patients (8.9 %) opting for surgery after six cycles of chemotherapy. This may overestimate the prognostic impact of bowel resection as patients undergoing interval procedures requiring multiple bowel resections probably had higher associated chemotherapy resistance. Median survival in patients with multiple bowel resections was of only 15 months. Jaeger et al. reported that bowel involvement in epithelial ovarian cancer had a bad prognosis and that survival could not substantially be improved by bowel resection, independently from the residual disease achieved.[9] Other studies have shown that multiple bowel resections are associated with poor prognostic outcome due to the increased risk of postoperative morbidity. Anastomotic leaks can have a negative impact on hospital length, delay in starting chemotherapy, and 90-day mortality and OS.[10] In our series, data were unavailable as postoperative morbidity and time to chemotherapy were potentially increased in patients with multiple bowel resections; however, higher postoperative 90-day mortality was not observed in these patients. Literature data addressing the question of the impact of bowel resection on outcome after cytoreduction remain unclear because of the lack of uniform data showing improved survival.[11] Several series also support survival benefit in patients with extensive upper abdominal disease requiring radical cytoreductive procedures when compared with patients completely cytoreduced by less aggressive surgery.[12–14] MSKCC experience demonstrated that complete cytoreduction decreases the risk of recurrence and death irrespective of the initial presence and volume of upper abdominal tumor burden present at the beginning of surgery.[4] The benefit of complete surgery remains even after occurrence of recurrent disease.[2]

Hamilton et al. have recently addressed this question by evaluating 417 advanced ovarian cancer patients with no

TABLE 2 Prognostic factors after complete cytoreduction

Univariate analysis	HR (95 % CI) DFS	*p* value (log-rank)	HR (95 % CI) OS	*p* value (log-rank)
Stage				
IIIC	1.00	**0.002**	1.00	**0.010**
IV	1.65 (1.19–2.30)		1.76 (1.13–2.75)	
Upper abdominal procedure				
0	1.0	**0.0161**	1.00	0.18
0–25	1.39 (1.05–1.84)		1.31 (0.87–1.96)	
>25	1.52 (1.08–2.12)		1.52 (0.94–2.46)	
Surgical complexity				
Standard staging	1.00	**0.0001**	1.00	**0.018**
One visceral resection	1.65 (1.23–2.21)		1.38 (0.90–2.14)	
Two or more visceral resections	1.9 (1.44–2.51)		1.75 (1.18–2.60)	
PCI score[a]	1.03 (1.01–1.06)	**0.001**	1.03 (0.99–1.06)	0.068
Upfront versus interval surgery				
Upfront surgery	1.00	**0.0226**	1.00	0.155
Interval surgery (three to four cycles)	1.41 (1.07–1.84)		1.47 (0.99–2.17)	
Surgery after six cycles	1.52 (1.05–2.20)		1.21 (0.68–2.17)	
Multivariate analysis	**HR (95 % CI) DFS**	***p* value (wald)**	**HR (95 % CI) OS**	***p* value (wald)**
Stage				
IIIC	1.00	0.092	1.00	**0.014**
IV	1.43 (0.94–2.16)		1.76 (1.12–2.76)	
Upperabdominal procedure[b]				
0	1.00	0.806	NA	NA
0–25	0.94 (0.55–1.55)	0.740		
>25	0.89 (0.44–1.69)			
Surgical complexity				
Standard staging	1.00		1.00	
One visceral resection	1.71 (0.96–3.02)	0.062	1.46 (0.94–2.26)	0.089
Two or more visceral resections	2.01 (1.09–3.71)	**0.024**	1.70 (1.15–2.54)	**0.008**
PCI score[a]	1.01 (0.97–1.05)	0.748		
Upfront versus interval surgery				
Upfront surgery	1.00	0.248	NA	NA
Interval surgery (three to four cycles)	1.26 (0.85–1.85)	0.253		
Surgery after six cycles	1.51 (0.75–3.04)			

Bold values indicate the significant if $p < 0.05$

HR hazard ratio, *CI* confidence interval, *DFS* disease-free survival, *OS* overall survival, *PCI* Peritoneal Cancer Index, *NA* not applicable

[a] Treated as a continuous variable

[b] Upper abdominal procedure: defines volume of upper abdominal disease, in mm

residual tumor after CRS. Patients with upper abdominal disease and no residual tumor after surgery had a poorer prognosis than similarly staged patients whose initial disease burden did not involve the upper abdomen.[15] Hoskins et al. [Gynecologic Oncology Group (GOG) 52] found similar results, and concluded that initial extra-pelvic disease remained a significant predictor of decreased survival.[16] The MSKCC series including 526 patients found decreased PFS and OS with increasing initial tumor burden, suggesting more aggressive biological disease or disease for a longer period of time. However, significant survival benefit was still observed in high-risk groups after CRS.[4]

In the present study, tumor extension, as measured by the PCI, was the only significant prognostic factor associated with decreased DFS in patients who underwent complete upfront surgery. Other reports have identified clinical markers of decreased survival, even when complete

CRS is achieved. In a previous study, positive coeliac lymph node involvement in patients with peritoneal carcinomatosis defined a less favorable patient subgroup which was associated with poor oncologic outcome and resistance to platinum-based chemotherapy.[17] The European Organisation for Research and Treatment of Cancer (EORTC) 55971 randomized trial demonstrated that the combined analyses of tumor size and clinical stage were significantly associated with treatment benefit and 5-year survival.[18] Treatment strategy based on both markers was proposed for stage IIIc and IV ovarian cancer by selecting stage IIIc patients with the largest metastatic tumor ≤45 mm to primary surgery, stage IIIc patients with the largest metastatic tumor >45 mm or stage IV patients with the largest metastatic tumor ≤45 mm to either surgery or neoadjuvant chemotherapy, and patients with clinical stage IV and the largest metastatic tumor >45 mm to neoadjuvant chemotherapy.[18] The authors stated that this strategy could improve 5-year survival in more than 6 % in the corresponding patient population. Marginally better survival has also been found in patients randomly assigned to primary debulking with metastases smaller than 5 cm.[18] In the present study, size of upper abdominal disease was also related to PFS in univariate analysis.

Surgical practice has demonstrated that most disease locations are amenable to cytoreduction with improved survival and reasonable morbidity.[19] In our series, surgical complexity was an independent marker of OS when complete surgery was achieved, which may be explained by the selection of patients with poor response to chemotherapy at the time of interval surgery. This suggests that surgical effort is not enough to compensate tumor biology; however, negative prognostic impact of complex procedures was not seen in patients undergoing upfront surgery.

Horowitz et al. reported that patients with the highest disease burden defined by upper abdominal disease had significantly shorter DFS (18.3 vs. 33.2 months) and OS (50.1 vs. 82.8 months) compared with those with moderate or low disease burden after complete cytoreduction.[20] In the present series, DFS after complete upfront surgery was 24.1 months, inferior to that reported in some studies.[21,22] This may be explained by the population-based study including a high proportion of patients with upper abdominal disease referred from other institutions. DFS after complete interval surgery at three cycles was 19.1 months, and 16.9 months after six cycles of chemotherapy. Horowitz et al. reported that only 199 patients from the 1636 patients with high disease burden who were included in the study (12 %) were completely cytoreduced. In our series, 64 % of patients with high disease burden or upper abominal disease were completely cytoreduced. The rate of upper abdominal procedures required in our study was similar to previous reports. In this series, the rate of diaphragm strippings, splenectomies, hepatic resections, and porta-hepatis procedures were similar to those reported by the two largest series of upper abdominal surgery in which 13–35 % of diaphragm procedures, 4–12 % of splenectomies, 0.5–4 % of pancreatectomies, 4–6 % of hepatic resections, and 0.2–5 % of porta-hepatis procedures are described.[23,24] As in previous series, the right diaphragmatic procedure was the most common upper abdominal procedure.

Primary cytoreduction with complete resection followed by adjuvant chemotherapy is the mainstay of advanced ovarian cancer treatment. Even when complete resection can be achieved in patients with good performance status, other criteria should be incorporated in the clinical signature to predict a patient's outcome. It is important to integrate extension of disease, surgical complexity, including number of visceral resections required, and associated morbidity and mortality in order to improve treatment strategy.

Limitations of this study include its retrospective nature, and the absence of morbidity and mortality data of surgical procedures. Sample size was small and was also limited by heterogeneous treatment strategies, including patients who underwent upfront surgery, interval debulking, HIPEC, and postoperative intraperitoneal chemotherapy. There is also a potential bias in the proportion of patients with platinum resistance in the present study as refractory patients who did not undergo debulking surgery were not included in the analysis. In this series, the rate of patients who received neoadjuvant chemotherapy is high, which can be explained by the high proportion of patients referred to our institutions after external evaluation and once neoadjuvant chemotherapy had been previously started.

CONCLUSIONS

Stage IIIC–IV ovarian cancer patients who require successful complete cytoreduction by complex surgical procedures had worse outcome than patients requiring standard procedures. The negative impact of surgical complexity was not significant in patients who underwent upfront procedures. Extensive disease requiring two or more visceral resections to obtain complete cytoreduction at the time of interval debulking was an independent poor prognostic factor and probably reflects a more aggressive behavior. Standard platinum- and taxane-based adjuvant chemotherapy do not seem to be adapted to this subgroup of patients, and specific adjuvant strategy should be considered. Tumor volume and extension was associated with decreased DFS in patients who underwent upfront surgery.

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