short review

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Ovarian cancer surgery

Game-changing innovations

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Summary Surgery is a cornerstone of treatment in patients with ovarian cancer. In primary disease, patients should be carefully selected to undergo either primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery. The aim of every debulking surgery is complete tumour resection. Whilst thorough evaluation of the iliac and para-aortic lymph nodes is important, systematic lymphadenectomy may be omitted when lymph nodes seem unsuspicious. To date, surgical outcome seems to remain the most important prognostic factor in the treatment of patients with ovarian cancer and therefore patients should only be treated in high-volume centres that are able to perform complex multidisciplinary surgery. The role of debulking surgery in recurrent disease has yet to be defined.

Keywords Gynecological oncology · Debulking surgery · Recurrent ovarian cancer · Secondary cytoreductive surgery · Lymphadenectomy

Introduction

Ovarian cancer is the second most common gynaecologic cancer in developed countries and is associated with high mortality rates [1]. The current standard of ovarian cancer treatment consists of a combination of primary cytoreductive debulking surgery and adjuvant platinum-based chemotherapy. Although recent advances in systemic chemo- and antibody therapy have improved (progression-free) survival (PFS) significantly [2–4], surgery remains the main cornerstone of ovarian cancer treatment. The aim of cytoreductive debulking surgery is to resect all visible tumour masses in total because complete resection of the tumour is significantly associated with overall survival (OS; Fig. 1; [5]). When complete cytoreduction is achieved, the 3-year overall survival is 72.4%, whereas in patients with macroscopic residual disease the 3-year overall survival is only 45.2% ($p<0.001$) [6]. This is valid for patients treated with upfront surgery or interval debulking surgery. Even in the era of anti-angiogenetic treatment and PARP inhibition, the surgical outcome seems to remain the most important prognostic factor in ovarian cancer treatment. Since ovarian cancer is a vastly aggressive tumour often showing remarkably fast growth complete cytoreduction is frequently virtually impossible. Therefore patients should be treated at centres with high case load that are able to perform complex multidisciplinary surgery [7].

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Primary disease

Early stage disease

Role of minimally invasive surgery

In early stage disease, surgical staging with adjuvant chemotherapy is standard of care. According to the ESMO and ESGO guidelines, laparotomy is recommended as a surgical approach to minimize the potential risk of tumour rupture [8]. In early stage disease in particular, several approaches have been made to introduce minimally invasive surgery as staging method [9]. However, to date no high-quality data from randomized clinical trials have been published; therefore laparotomy remains standard of care [10]. Though, in cases of restaging surgery, since

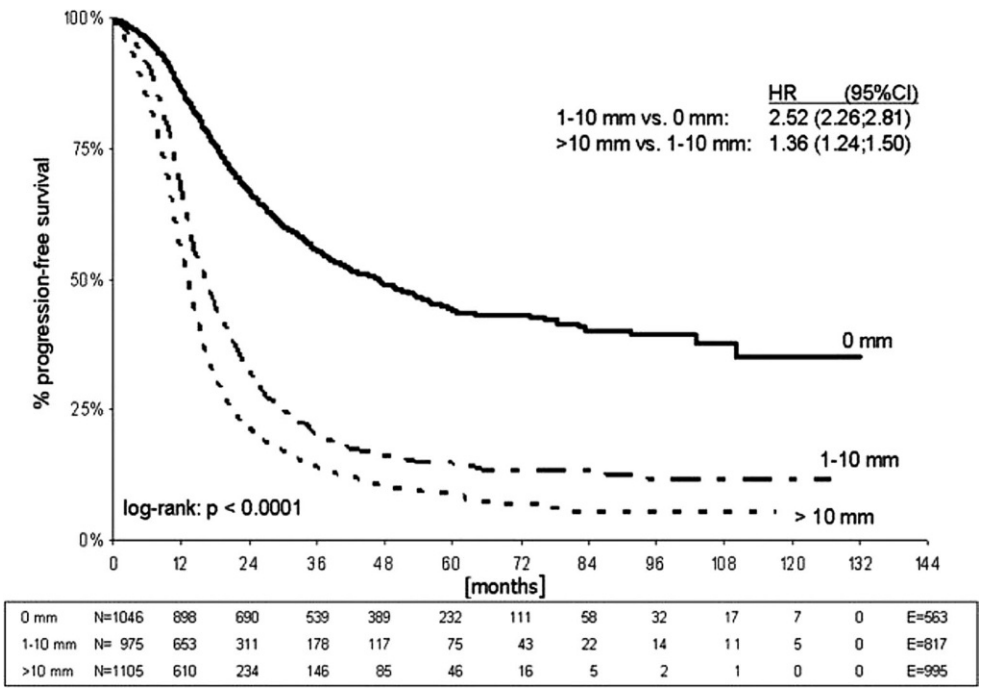

Fig. 1 Overall survival of patients with ovarian cancer according to size of residual tumour (from [5]. By courtesy of John Wiley & Sons, Inc.)

the tumour is already resected and there is no risk of tumour spread minimally invasive surgery may be offered. Exploration of the complete peritoneal cavity, pelvic/para-aortic lymphadenectomy and infracolic omentectomy might be challenging when performed by laparoscopy; hence it should only be offered by trained surgeons in expert centres to assure optimal results.

Regardless of the surgical approach, optimal surgical staging is of utmost interest. Solely after optimal surgical staging, in case of FIGO IA G1/2 tumours, adjuvant chemotherapy can be safely omitted [8]. If surgical staging is inadequately performed, patients have to undergo chemotherapy independent of tumour stage.

Advanced disease

Use of primary debulking surgery (PDS) + adjuvant CHT vs. neo-adjuvant chemotherapy with interval debulking surgery (NACT+IDS) in advanced disease

Several trials investigated the value of PDS compared to three cycles of NACT+IDS followed by three additional cycles of CHT. Several retrospective studies showed significant survival advantage of patients undergoing PDS compared to NACT+IDS in patients with advanced ovarian cancer. Therefore, it was rather surprising in 2010 when a prospective randomized controlled trial that investigated this issue showed no benefit of PDS compared to NACT-IDS (EORTC55971) [11]. In addition, this study showed significantly higher rates of adverse events in patients undergoing PDS compared to NACT-IDS. In addition, the CHORUS study published in 2015 investigated the same issue and again revealed no advantage of PDS vs NACT+IDS in patients with advanced ovarian cancer [12]. However, when compared with cohorts from other randomised trials complete resection rates and survival outcome was poor in both arms of the study [13]. In addition, both studies were criticised for statistical and conduction flaws. Therefore, the German AGO launched an international collaborative trial (TRUST, NCT02828618). In this trial, only high-volume gynaecologic oncology departments are included and treat ovarian cancer patients with PDS or NACT-IDS in a randomized controlled fashion. This study has already closed participant accrual in 2019 and the results of the trial are highly anticipated.

Anyhow, an attempt of surgical exploration and cytoreduction should be performed in any patient who tolerates surgery. Sole CHT treatment should be restricted to a small numbers of patients and has to be considered a palliative treatment strategy [8].

Role of minimally invasive surgery

In advanced stage disease, minimally invasive surgery may be used as diagnostic tool to assess the extent of disease and guide the decision between PDS vs. NACT+IDS. For this use, the Fagotti scoring system might be used [14]. The Fagotti score is an objective quantitative laparoscopy-based model to predict the chances of optimal cytoreductive surgery in patients with advanced ovarian cancer. The scoring model includes a total of seven items and when performed correctly, it delivers a very high positive predictive value and a modest negative predictive value for optimal de-

bulking. However, one has to consider the high rate of port-site metastases, which has been observed after diagnostic laparoscopy [15].

Lymphadenectomy

For decades, pelvic and para-aortic lymph nodes have been removed systematically during cytoreductive surgery regardless of their clinical appearance and without supporting evidence from randomized clinical trials. Systematic pelvic and para-aortic lymphadenectomy is a complex, time-consuming procedure associated with significant short- and long-term adverse effects. Therefore, in the LIONS systematic pelvic and para-aortic lymphadenectomy was investigated in patients with advanced stage epithelial ovarian (>FIGO IIb) cancer patients who underwent PDS [13]. In patients, where a complete tumour resection was achieved and lymph nodes were clinically unsuspicious, patients were randomized to either complete systematic pelvic and para-aortic lymphadenectomy, or no lymphadenectomy. This trial included a total of 647 patients and the primary endpoint was OS. Within the cohort 55.7% of patients had involved lymph nodes on histologic evaluation, although imaging and clinical intraoperative assessment did not identify lymph node metastases. Interestingly, in this study patients who had lymphadenectomy showed an OS of 65.5 month compared to 69.2 month in patients who had not received lymphadenectomy (HR 1.06, 95%CI 0.92–1.34; $P=0.29$). While lymphadenectomy did not show a survival benefit, patients who underwent lymphadenectomy were significantly more likely to experience serious postoperative complications and even postoperative death (3.1% vs. 0.9%, $p=0.049$). Therefore, in patients with advanced ovarian cancer who show unsuspicious lymph nodes before and during surgery lymphadenectomy should be avoided.

Recurrent disease

Currently, there is an ongoing discussion whether patients with recurrent disease benefit from second cytoreductive surgery. Data from retrospective studies suggest a survival benefit from surgical resection [16], but evidence from prospective randomized trials have been limited until recently.

The German Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) has performed a series of studies on this matter.

The retrospective AGO DESKTOP OVAR I study was performed to guide the decision whether to perform or not perform secondary cytoreductive surgery in patients with recurrent ovarian cancer. The 3 selection criteria were defined as no residual tumour after primary debulking surgery (1), absence of ascites (2) and an ECOG performance status of 0. These three variables comprise the AGO score. If all selection criteria were fulfilled, complete tumour resection during secondary cytoreductive surgery was 79% [17].

The AGO DESKTOP II study was consecutively performed to prospectively validate the results from the AGO DESKTOP I trial [18]. In this study, 129 patients with platinum-sensitive recurrent ovarian cancer that fulfilled the AGO score were included. All patients had secondary cytoreductive surgery and complete resection was achieved in 98 patients (76%), confirming the results of the DESKTOP I study.

Consequently, the German AGO conducted the AGO Desktop III study and recently reported results of an interim analysis regarding the PFS (ASCO 2017, Abstract 5501).

This study included patients with recurrent epithelial ovarian cancer who fulfilled all criteria according to the AGO score. In total 409 patients were screened, and 407 patients were included into the trial. Patients were randomized to either secondary cytoreductive surgery or no surgery. All patients received platinum-based chemotherapy.

This study showed that secondary cytoreductive surgery was safe, feasible and yielded a complete tumour resection rate of 72.5%. The PFS was 21.2, 13.7 and 14.0 months in patients were complete resection was achieved, in patients with incomplete tumour resection and patients who did not undergo surgery, respectively. Therefore, if complete resection was achieved, patients had a significant prolongation of PFS of 7.2 months compared to patients who had incomplete resection or no surgery ($p<0.00001$). Time to third line chemotherapy was also significantly longer in patients who had complete tumour resection. However, the primary endpoint of this trial was OS, and the final data are still immature. Therefore, the final results of the DESKTOP III trial are highly anticipated.

On the contrary, another randomized prospective trial has also reported results on secondary cytoreductive surgery, recently. The GOG-213 protocol included a total of 1052 patients with recurrent ovarian cancer who had a complete response to first-line treatment and a treatment-free interval greater than 6 months. Within this study a subgroup of 485 patients were randomized to either secondary cytoreductive surgery ($n=240$) or no surgery ($n=245$). In a second step these patients were then randomized to receive platinum-based chemotherapy either with or without bevacizumab (15 mg/m^2). Interestingly, this study failed to show a benefit of secondary cytoreductive surgery compared to no surgery regarding both the PFS (median PFS 18.9 vs. 16.2 months, HR 0.82; 95%CI 0.66–1.01) OS (median OS 50.6 vs. 64.7 months, HR 1.29; 95%CI 0.97–1.72). However, similar to the results of the AGO DESKTOP III study a significant difference in PFS in favour of surgery was shown in patients that had complete tumour resection during secondary cytoreductive surgery compared to patients who did not undergo surgery (median PFS 16.2 vs.

22.4 months; HR 0.62; 95% CI 0.48–0.80). Interestingly, adverse events were similar in both study arms [19].

Conclusion

Cytoreductive surgery remains the mainstay of treatment in patients with advanced ovarian cancer. While current evidence suggests that NACT+IDS is comparable to PDS, the final words on this subject have yet to be spoken. Hopefully, the ongoing TRUST trial will give the final answer to this important question. The LIONS trial showed that systematic lymphadenectomy can be safely omitted in patients with unsuspicious lymph nodes during cytoreductive surgery for primary advanced ovarian cancer. In recurrent disease there is an ongoing discussion regarding the value of secondary cytoreductive surgery. While the GOG-213 trial failed to show a benefit in overall survival from secondary cytoreductive surgery, both the GOG-213 protocol and the AGO DESKTOP III trial show a significant benefit in PFS in patients with complete tumour resection. Still, final (overall survival) results of the AGO DESKTOP III trial are pending and highly anticipated.

Take home message

Cytoreductive surgery is the cornerstone of ovarian cancer treatment. Since complete tumour resection is the most important prognostic factor in patients with ovarian cancer, surgery should always be performed by a certified gynaecologic oncologist in a high-volume centre.

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Conflict of interest R. Schwameis, V. Paspalj, M. Kranawetter, and S. Polterauer declare that they have no competing interests.

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