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Whole abdomen irradiation in epithelial ovarian cancer – state of the art

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Epithelial ovarian cancer (OC) as a malignancy which poses multiple challenges has led to growing attention and concern during recent years. The not very noteworthy treatment results achieved during the last three decades with contemporary chemotherapeutic schemes have led to the need for research and development of new therapeutic approaches, as well as to a resurgence of interest in radiotherapy (RT) as part of a combined modality approach and as salvage therapy for patients with small volume persistent disease after primary cytoreductive surgery and chemotherapy. This article reviews the state of the art of whole abdomen irradiation (WAI) (excluding the moving strip field technique) as part of the complex treatment of epithelial OC. The prognostic factors and risk groups of epithelial OC are discussed as indicators for WAI, giving in detail the applied treatment modalities, fractionation and total doses. Toxicity and second primary malignancies following WAI are analyzed. The clinical experience accumulated during the last decades, as adjuvant, consolidative, salvage and palliative WAI in combined treatment of epithelial OC, is presented. Current issues in the radiotherapeutic management are discussed along with ideas for future clinical research directions.

Key words: epithelial ovarian cancer, radiotherapy, whole abdomen irradiation, state of the art.

Ovarian cancer (OC) is the fourth most frequent fatal malignancy in women and the leading cause of death from gynaecological malignancies. It is a life-threatening diagnosis which has continued to be a cause of grave concern over decades.

A large majority of ovarian malignancies, 85% to 90%, arise from the surface layer or epithelium. Epithelial OC is a heterogeneous disease and many biological and molecular factors are important for its development and progression, including growth rate, metastatic potential, and chemo- and radiosensitivity. Even in the early stages of the disease many questions about its biological behaviour, optimal treatment, and prognosis continue to be a problem of great consideration for the oncoradiology community.

Although important advances have been made during the last 3 decades in surgery, chemotherapy (CT), and radiotherapy (RT), overall survival (OS) for patients with OC has not changed significantly. Despite the improved surgical techniques as many as 20% of women with early stage disease will eventually relapse and die from their disease. The postoperative management of OC also remains controversial. Paclitaxel and platinum CT is still the treatment of choice after primary debulking surgery [l–3]. Regardless of the certain improvements seen in OS using a combination of these chemotherapeutics, long-term survival rates for patients with advanced OC remain disappointing [4–6]. They have also failed to show a significant advantage compared with results achieved by the use of external beam radiotherapeutic modalities [7, 8].

Unfortunately the past years have not seen any breakthroughs in radiation treatment of gynaecological cancer either. The proper role of RT in the management of OC is still not clearly established despite its long history in the treatment of the disease. Whole abdomen irradiation (WAI) as a primary postoperative therapy after a comprehensive surgical staging in completely resected stages of OC has been used worldwide less frequently despite the proven curative role in patients with microscopic or minimal residual disease. Similarly, the potential role of WAI as consolidative treatment and as salvage therapy following CT failure remains controversial.

However, the not very noteworthy treatment results achieved during the last decade with contemporary chemotherapeutic schemes have led to the need for research and development of new therapeutic approaches, as well as to a resurgence of interest in RT as part of a combined modality approach and as salvage therapy for patients with small volume persistent disease after primary cytoreductive surgery and CT.

The aim of this review article is to discuss the state of the art of WAI (excluding the moving strip field technique) as part of the complex treatment of epithelial OC.

Prognostic factors and risk groups of epithelial ovarian carcinoma as indicators for whole abdomen irradiation

The risk groups of epithelial OC have been well known for more than two decades. As early as in 1982 Dembo separated patients with OC into three

distinct risk groups on the basis of stage, postoperative residual tumour volume, and grade [9–12]. In 2005 Dinniwell *et al.* modified the prognostic classification developed by Dembo by adding to the low, intermediate and high risk groups the so-called ultra-high risk groups, which include FIGO Stage III OC with abdominal residuum [13].

Several factors have been identified as possible prognosticators in early-stage disease, comprising stage I disease with grade 1 patients, the so-called low-risk group, as well as stage I disease grades 2 and 3, belonging to the intermediate-risk group. For these groups adjuvant WAI is one option among other treatment modalities (e. g. no further treatment or various types of CT). On the basis of a study on 642 patients with stage I disease, in 1990 Dembo determined for these groups degree of differentiation, presence of dense adhesions between the tumour and pelvic organs, and presence of ascites as independent prognostic importance [11]. No further treatment is indicated in patients with stage I, grade 1 tumours and no ascites or adherence of tumour in the pelvis which have at least 90% long-term disease-free survival (DFS) following surgery alone [11, 14]. According to the contemporary concepts, in patients with well differentiated stage I OC, DNA flow cytometric analysis may indicate a subgroup with less favourable prognostic characteristics (DNA ploidy), which has been acknowledged for two decades as an important independent prognostic factor [15, 16]. Poorly differentiated tumours have clearly demonstrated a worse prognosis. The evidence for this is the significant difference in the achieved survival rates in patients with stage I disease with grade 1, 2 or 3 tumours (96 : 78 : 62%, respectively [12]. According to the Gynecologic Oncology Group (GOG) and to randomized trials of Dembo [10, 11, 14, 17], tumour size, tumour bilaterality, capsular penetration, cyst rupture, histological subtype or type of postoperative therapy showed no correlation with survival or increased risk of relapse. However, other authors presume that histology of epithelial OC does reflect stage at presentation, degree of differentiation and tumour burden [18]. Patients with mucinous and endometrioid cancers have a higher survival rate, while there are controversial opinions for clear cell cancers [13, 19].

The intermediate-risk group constitutes nearly 33% of all patients with OC. The main part of this subgroup represents patients with stage I and II disease. This group, in which WAI is recommended as the sole postoperative treatment, is selected based on grade, stage and presence of pelvic residual disease. Volume of residual after primary surgery strongly correlates with survival [20, 21]. Patients with stage III, grade 1 disease that are optimally debulked (< 2 cm) and who have residual disease located only in the pelvis on laparotomy may be considered for WAI as well [21].

The patients with higher stage, high grade disease constitute the high-risk group. An ultra-high-risk group encompasses patients with gross abdominal residuum at the completion of surgery. The two groups, which are not suited for WAI as a sole treatment, usually require aggressive CT [22].

Apart from tumour ploidy, oncogene amplification may also influence survival of epithelial OC. More extensively studied are two important growth factor receptors for oncogenesis (HER-2/neu and EGFR) [23, 24]. While the attitude to HER-2 positivity is controversial, the EGFR status of the tumours has been accepted as an independent and significant prognostic factor. Positive EGFR staining has been associated with poor survival. The forthcoming therapeutic strategy for epithelial OC might be to decrease EGFR expression by gene therapy in combination with adjuvant RT and/or CT.

Whole abdomen irradiation

Treatment modalities

RT which is offered as an adjuvant to surgery of OC should be designed to include strategies incorporating all anatomical sites at risk for disease dissemination. Compared with other solid tumours the unique pattern of dissemination is especially typical for OC. The RT treatment should include the entire peritoneal or abdominal cavity. As a result, techniques using WAI or instilled intraperitoneal radioisotopes have evolved into the most commonly prescribed treatment programmes.

The planning target volume (PTV) for WAI includes the entire abdomen and pelvis, from the diaphragm to the floor of the pelvis and laterally to the abdominal sidewalls. All peritoneal surfaces, abdomino-pelvic lymphatics, and the undersurface of the diaphragm should be treated. As early as in 1992 Dembo, in his prospective study from the Princess Margaret Hospital, emphasized the necessity of covering the diaphragm with an appropriate margin during all phases of normal respiration [25]. Doses to the organs at risk such as liver and kidneys should be maintained below the respective whole-organ tolerance doses. Computed tomography guided treatment planning is not critical in defining therapy fields. It may better define the blocking and dosing requirements for critical organs in the PTV.

During the last 30 years, after the gradual abandonment of the moving strip technique in routine RT practice, various other large field radiation techniques have been applied for WAI. Einhorn *et al.* introduced at Radiumhelmet in Stockholm in 1976 a six-field radiation technique [26, 27]. The treatment was divided into three phases. In the first phase the whole abdomen was irradiated with 20 Gy using 1.2 Gy/fraction. The second phase, which was started immediately, included irradiation of the lower abdomen with 20 Gy – 1.6 Gy/fraction. The third phase of irradiation included the cranial part of the abdomen with two opposed lateral fields to a dose of 20 Gy – 1.6 Gy/fraction. Using this technique, 80% of the upper part of the abdominal compartment received a dose of 40 Gy, the lower abdomen also received 40 Gy, and the absorbed dose to the remaining 20% of the compartment including two thirds of the kidneys and one half of the liver ranged from 20 to 40 Gy.

Subsequently the basic techniques used for WAI presented in chronological order are those of Martinez *et al.* [28], Kuten *et al.* [29], Calkins *et al.* [30] and Thomas *et al.* [31]. The so-called open field technique of Martinez *et al.* includes AP-PA fields with a 1 to 2 cm margin for the entire abdomen and pelvis [28]. They are treated at

1.5 Gy per day to 30 Gy. In phase two fields are reduced to include the medial diaphragms, periaortic lymph nodes, and whole pelvis. These fields are treated to 42 Gy at 1.5 Gy fractions. The final phase treats only the true pelvis at 1.8 Gy to a 51 Gy total dose. Kuten uses a split-field technique, in which 30 Gy are delivered in sequential fashion to the upper portion of the abdomen and pelvis [29]. Calkins uses a delayed split WAI technique allowing the entire tumour volume to be irradiated with tumoricidal fractional doses without undue toxicity [30]. The upper hemiabdomen is irradiated with 1.5 Gy per fraction to a total dose of 30 Gy. The lower hemiabdomen is irradiated with 2 Gy per fraction to a total dose of 40 Gy. A 2-6 hour delay is used between the irradiation of each half of the abdomen to avoid excessive acute gastrointestinal toxicity. Shielding of the iliac crests spares bone marrow, allowing delayed split WAI to be integrated into an aggressive combined modality treatment plan. Thomas *et al.* use a four-field orthogonal technique to deliver 30 Gy at 1.5 Gy fractions over 30 days to the whole peritoneum [31]. Boosts to the abdominal lymph nodes and the pelvis up to 15 Gy are used. In all of the above-mentioned techniques for WAI the kidneys and liver are blocked to minimize dose.

In the first years of the new century whole abdomen intensity-modulated radiation therapy (IMRT) has been implemented with the aim of achieving better PTV coverage with improved sparing of organs at risk [32-34]. Hong *et al.* have developed a process to plan and deliver IMRT using standard linear accelerators and dynamic multileaf collimators [32]. Rochet *et al.* also describe a whole abdomen IMRT technique using helical tomotherapy [34]. The PTV, including the entire peritoneal cavity, was adapted according to breathing motion as detected in four-dimensional respiratory-triggered computed tomography. According to the authors helical tomotherapy enabled a very homogeneous dose distribution with excellent sparing of organs at risk (kidneys, liver, bone marrow, spinal cord, thoracic and lumbosacral vertebral bodies, and pelvic bones) and coverage of the PTV.

Fractionation

Conventional, single daily dose of 1 to 1.8 Gy regimens to a total dose of 45 to 50 Gy appear to be most commonly used by WAI during the last decades [26-31].

Theoretically hyperfractionated RT would increase cell death by limiting repopulation, decreasing relapse rates and improving tolerance while minimizing abdominal late reactions. The known hyperfractionated therapy programmes for WAI are those developed by Kong *et al.*, Fein *et al.*, Eifel *et al.* and a number of other authors [35-38]. Kong *et al.* and Eifel *et al.* used a split-course technique of 1 Gy in twice-daily fractions to a total dose of 30 Gy [35, 36]. A planned 3-week mid-therapy break was given. A boost over 30 Gy was given only to patients with gross residual disease. Fein *et al.* used a continuous hyperfractionated RT with 0.8 Gy twice daily to doses of 35.2 Gy [37]. Later total doses were reduced to 30.4 Gy because of toxicity. A pelvic boost of 0.8 to 1.2 Gy twice daily was used to an additional 14.6 Gy.

A hypofractionated radiation treatment regimen prospectively studying the palliative effect in patients with chemoresistant OC was used by Faul *et al*. [39]. Patients were treated with a single radiation fraction (7 Gy) or with two fractions (3 Gy twice a day) to the abdomen over 1 day.

Total doses

In WAI the most frequently applied doses are of approximately 30 Gy delivered to the entire peritoneum with a whole pelvis boost to a total dose of 45 to 50 Gy. There are controversial opinions concerning the influence of the total dose magnitude on the therapeutic effect of WAI [40, 41].

Fyles *et al.* carried out a prospective randomized clinical trial of two doses (22.5 Gy and 27.5 Gy) of WAI on 125 patients with debulked stage I-III OC [40]. OS and DFS at 5 years in the low and high dose arm were 83% : 72% ($p = 0.3$) and 74% : 67% ($p = 0.5$), respectively. There was no difference in survival, tumour control, or toxicity between high-dose and low-dose WAI. According to the authors high-dose WAI is unlikely to be associated with an increase in OS of more than 4% or DFS of more than 9%.

Firat *et al.* have another attitude [41]. The opinion of the authors for the intermediate-risk group investigated by them, in which the established 5- and 10-year OS rates after the applied WAI were 61% and 54%, was that a total abdominal dose of ≥ 36 Gy is associated with a longer OS independent of stage, grade, and amount of residual disease. This is most likely due to a significant reduction in the incidence of abdominal recurrence in patients receiving > 36 Gy to the whole abdomen (18% vs. 49%, $p = 0.006$). Multivariate analysis revealed abdominal dose ($p = 0.018$) as an independent factor influencing the rate of abdominal recurrence. The results of this study suggest a possible dose-control relationship between the whole abdominal dose and the risk of abdominal recurrence.

Toxicity and second primary malignancies following whole abdomen irradiation

The use of large radiation fields, such as those implemented in WAI, which incorporate multiple abdominal organs, contributes to the development of predictable side effects. The assessment of acute and late toxicity from WAI conducted as a sole or as part of a combined treatment, represents a topic of a number of clinical trials. It is generally acknowledged that in this large field technique acute toxicity is common but infrequently severe and late toxicity is acceptable and predictable.

One of the earlier studies in this respect (between 1971 and 1985) of Fyles *et al.* on 598 patients treated with abdomino-pelvic RT including moving strip and open field technique is of special interest [42]. Acute complications included nausea and vomiting in 364 patients (61%), which were severe in 36, and diarrhoea in 407 patients (68%), severe in 35. Leukopenia (< 2.0×10^9 cells/l) and thrombocytopenia (< 100×10^9 cells/l) occurred in 64 patients (11%). Treatment interruptions occurred in 136 patients (23%) and 62 patients (10%) did not complete treatment. In both situations the most common cause was

myelosuppression. Late complications included chronic diarrhoea in 85 patients (14%), transient hepatic enzyme elevation in 224 (44%), and symptomatic basal pneumonitis in 23 (4%). Serious late bowel complications were infrequent: 25 patients (4.2%) developed bowel obstruction and 16 required operation. Fyles *et al.* concluded that abdomino-pelvic RT as used in these patients was associated with modest acute complications and a low risk of serious late toxicity.

The authors of a number of subsequent trials confirmed the described acute and late toxicity of WAI open field technique [43-45]. The immediate tolerance to radiation is considered by the French colleagues at Centre Vauntin in Nancy as globally satisfactory since 9% of the patients had no problems and 64% of the patients developed a minor intolerance easily controlled by symptomatic treatment [45]. Quetin *et al.* evaluated in more detail late irradiation sequelae of WAI for 89 patients with a follow-up lasting from 4 months to 11 years. Five patients presented severe complications, including haematological problems such as chronic thrombopenia in two cases, and one patient represented a case of histologically proven malabsorption. Two patients exhibited major problems – one case of radic cystitis and one of radic bowel. Two patients died of iatrogenic causes – one of induced leukaemia, the other of treatment-induced digestive and renal complications. Similar results for major bowel complications from 1098 patients in 10 series include bowel surgery (5.6%) and deaths (0.4%) [46].

The renal and hepatic toxicity developed after sole WAI or combined with CT deserves special attention. According to Irwin *et al*. there is no evidence of late renal toxicity more than 5 years after WAI with a mean renal dose of 19.28 Gy [47]. Schneider *et al*. concluded however that the decline in renal function after WAI is more pronounced than in healthy subjects. Moreover, treatment with cisplatin and second-look laparotomy prior to WAI does not seem to contribute to this loss of kidney function [48].

The development of hepatic toxicity in the form of chylous ascites after WAI is also worth special interest. Distinguishing this clinical entity from recurrent OC is important because of its benign course and its resolution with conservative management. The study of Lentz *et al.*, who report eight patients with developed chylous ascites from the totally evaluated 207 patients with delivered WAI for gynaecological malignancies at the Mayo Clinic is also interesting in this respect [49]. Irradiation was done adjuvantly (five patients) or as salvage therapy after CT failure (three patients). Mean total radiation doses were 29.25 and 51.22 Gy to the abdomen and pelvis, respectively, with para-aortic boosts administered in six cases to a mean total dose of approximately 42 Gy. The mean time from completion of WAI to development of ascites was 12 months. The ascites resolved in all eight cases at a mean of 18 months after development.

Insufficiency fractures as a side effect of pelvic RT in postmenopausal women have become widely recognized in recent years and were probably underreported in earlier studies on WAI. The 7% incidence in the study of Dinniwell *et al.* is in keeping with the published literature for gynaecological malignancies [13, 50-52].

The impact of a number of RT factors (radiation technique, fractionation, total doses) on acute and late toxicity of WAI is also subjected to investigation. Multivariate analysis was unable to determine any significant prognostic factors for bowel obstruction, but the moving-strip technique of RT was associated with a significantly greater risk of developing chronic diarrhoea, pneumonitis, and hepatic enzyme elevation than was the open field technique [42]. Both the haematological and musculoskeletal side effects seen in patients may have been reduced by using IMRT to minimize the dose to normal structures outside of the peritoneal cavity [32, 34]. Complication rates of hyperfractionated RT were no greater than those reported for standard therapy [37]. The toxicity observed by Faul *et al*. for the prospectively studied palliative hypofractionated radiation treatment regimen in patients with chemoresistant OC also includes the most frequently observed symptoms [39]. According to Fyles *et al*. there was no difference in haematological toxicity or late complications between the dose of 22.5 Gy and 27.5 Gy [40]. However, according to Firat *et al*., a whole abdominal dose > 30 Gy and a pelvic dose > 50 Gy were associated with a significant increase in small bowel obstruction ($p = 0.01$) independent of other factors [41]. They also concluded that when greater abdominal doses and greater pelvic doses were combined a higher rate of small bowel obstruction was observed.

The impact on toxicity of combined treatment of OC, including most often carboplatin/paclitaxel CT and WAI, also represents an issue of interest and investigation. Most of the studies indicate that consolidative and salvage WAI can be administered safely after surgery and standard CT with acceptable acute and late toxicity [8, 13, 53]. The greater part of the patients experienced fatigue, moderate leukopenia and thrombocytopenia, and gastrointestinal side effects that were easily controlled with medications. Late toxicity infrequently includes development of bowel obstruction, symptomatic sacral insufficiency fractures or fistula.

During the last decade the possibilities of colony-stimulating factors for coping with haematological toxicity have been studied in the course of WAI. The study of Fyles *et al.* established that filgrastim (granulocyte colony-stimulating factor, G-CSF) is safe and effective in reducing neutropenic treatment interruptions during WAI in patients with OC. However, there was no clear benefit to its use, as thrombocytopenia became the dose-limiting toxicity, resulting in a risk of treatment interruptions and early termination of RT [54].

It is generally acknowledged that excess malignancies following OC represent both complications of curative therapies and underlying susceptibility states that have aetiological and clinical ramifications [55]. For both agents, RT and CT, the risk of developing second primary malignancies (SPM) continued to increase more than 10 years after treatment began [56]. Clinical studies on carcinogenesis after complex treatment, including WAI, are rather scarce. Dembo reported in four patients SPM following combined treatment including WAI (one ocular melanoma,

one breast cancer, one thyroid lymphoma, one endometrial cancer of different histology) [9-11]. Dent *et al.* updated a study by the National Cancer Institute of Canada Clinical Trials Group (NCIC–CTG) and studied the development of SPM following treatment of 257 patients with early stage OC, including WAI, melphalan or intraperitoneal 32P [57]. Second primary malignancies developed in 29 women (11%) after 2.229 person years of follow-up. This compares to 18.7 SPM, which would have been expected in this group of age-matched controls, and was statistically significant ($p = 0.018$). There was no significant difference in the total number of SPM between treatment arms.

Whole abdomen irradiation as part of the complex treatment of ovarian carcinoma

Adjuvant whole abdomen irradiation

Approximately 30% of patients with epithelial OC present with localized or early stage disease (belonging to the low and intermediate risk group patients), for which a sole adjuvant WAI is one option among others such as no further treatment or various types of CT.

At present, still there have not been identified subsets of patients with specific prognostic factors who do not require additional therapy after proper primary surgical staging. The only exceptions are the patients with stage I grade 1 or 2, for whom adjuvant therapy usually is not needed [11, 18, 58]. Patients with stage I grade 1 tumours and no ascites or adherence of tumour in the pelvis have at least a 90% long-term DFS following surgery alone [11, 14]. According to most authors no therapy has been shown to benefit patients with stage I grade 2, 3 tumours, although relapse risks of 20% to 40% justify postoperative treatment in this group [59]. To improve treatment response, patients with stage IC disease are recommended for adjuvant treatment, as are those with high-risk features including high grade, clear cell histology, dense adherence, ruptured capsule, intraoperative rupture, ascites, positive peritoneal washing and tumour on the ovarian surface [60]. This is supported by the results of Skirnisdottir *et al.*, who assessed the efficacy of WAI applied as adjuvant postoperative therapy in patients with FIGO stage IA-IC epithelial OC and established 5-year OS and cancer-specific survival (CSS) of 69% and 72%, respectively [61].

As early as in the 1990s, in a review of five separate case series Dembo demonstrated that patients who received WAI did not benefit from RT alone unless only microscopic disease was present at the start of adjuvant treatments [11, 25]. The 10-year relapse-free survival (RFS) and OS rates with microscopic disease achieved by him were comparable with those for patients with high risk earlier-stage disease. The survival rates after WAI for patients with high-risk stage I and optimally debulked stage II and III disease reported at that time by other authors range from 50% to 77% depending on the prognostic factors [17, 62, 63]. The relapse rates in the low-, intermediate-, and high-risk groups following WAI alone are approximately 10%, 30%, and 80%, respectively [10, 12].

As a result of low incidence of OC diagnosed in early stages, only a few randomized clinical trials have been performed of both systemic CT and WAI. Long-term survival rates of OC patients treated in postoperative randomized prospective trials comparing both treatment modalities rather often do not justify the assumed superiority of CT over RT. As early as in 1988 a randomized trial by the C-NCI Trials Group assigned 257 patients to receive melphalan, WAI or ^{32}P for high risk stage I or optimally debulked stage II or III OC [18]. Actuarial 5-year survival rates failed to demonstrate a statistically significant difference. WAI significantly reduced relapse risk in patients with stage I and II disease where tumours were densely adherent. The general estimate of a number of authors is that WAI appears to produce results equal to those of CT in early stage patients [35,36, 64-69]. However, others consider that short-term CT appears to be a safe treatment in comparison to WAI [22, 70].

The clinical experience accumulated over the decades proves that a significant part of the oncoradiology community accepts adjuvant WAI as an effective anti-tumour modality in epithelial OC.

Consolidative and salvage whole abdomen irradiation

In spite of the high initial response rates, a significant proportion of patients with early stage epithelial OC eventually fail after initial responses to CT. Further treatment with CT consisting of either the same combination or with second-line regimens has been ineffective in producing durable responses. Advanced OC, which is also largely incurable, turned out to be also a problem of major importance. Stage III OC has shown resistance to adjuvant CT following surgical cytoreduction. On the other hand, in vitro studies and clinical experience have suggested that patients with platinum-refractory epithelial OC exhibit cross-resistance to radiation. According to a number of authors salvage with RT in these patients is rare. However, many other authors do not agree with this statement and evaluate WAI as a consolidative or salvage therapeutic modality considering its feasibility, efficacy, and toxicity for these patient groups [71-73].

There are a number of trials investigating the therapeutic possibilities of WAI as a consolidative therapeutic modality for patients with epithelial OC. There are several retrospective studies describing WAI given after surgery and CT to a residual tumour volume less than 2 cm which are with contrasting conclusions. Most authors believed that RT should be placed after surgery and CT for small residual tumours less than 0.5 mm or for tumour detected microscopically [35, 38, 74, 75]. Other authors do not agree with this opinion [76-80]. The study of Sheng *et al.*, comparing the possibilities of sole CT and CT combined with RT in early stage OC, is of interest in this respect [81]. The 5-year actuarial survival rate was 78.3% for the patients receiving additional RT and 72.4% for those without additional RT. The recurrence rate was 32.2% with a median recurrence time of 34 months in the former group, 60.6% and 18.6 months for the latter. According to the authors RT did not confer a survival advantage in the treatment of stage I OC, but it could decrease the recurrence rate and delay onset of recurrence.

Several prospective randomized trials, proving the therapeutic potential of consolidative WAI, deserve interest. In the early 1990s in a consolidation randomized study conducted in Switzerland comparing WAI or no further treatment after surgery and CT, the RT arm showed 93% survival in patients receiving WAI, compared with 49% for patients who did not receive RT [82]. In patients with residual tumours no significant difference was found among the groups. Swedish-Norwegian patients of stage III OC who were tumour-free after surgery and CT were thereafter randomized by Sorbe *et al.* to further CT versus WAI versus observation only [83]. The overall 3-year survival rate showed a trend but not a statistically proven better outcome for the RT group. Seven years later in 2003 Sorbe *et al.* again compared in a prospective randomized trial consolidation treatment with RT or CT with no treatment in patients with epithelial OC, FIGO stage III, with complete surgical remission after primary cytoreductive surgery and induction CT [84]. In the subgroup with complete surgical and pathological remission, progression-free survival (PFS) was significantly ($p = 0.032$) better in the RT group (56% at 5 years) than in the CT group (36% at 5 years) and the untreated control group (35% at 5 years). OS was also most favourable in the RT group (69% at 5 years). The number of recurrences was the lowest in the RT group. The overall relapse rate was reduced by 33% and the pelvic recurrences by 43% by consolidation RT. Similar results were also reported by Pickel *et al.* – according to them the RFS and OS of patients who received adjuvant chemoradiotherapy were significantly higher than those of patients who received adjuvant CT only (68% vs. 56% at 2 years and 49% vs. 26% at 5 years, $p = 0.013$, and 87% vs. 61% at 2 years and 59% vs. 33% at 5 years, $p = 0.029$) [85]. The differences were most pronounced in patients with stage III disease (77% vs. 54% at 2 years and 45% vs. 19% at 5 years, $p = 0.0061$, and 88% vs. 58% at 2 years and 59% vs. 26% at 5 years, $p = 0.012$). From the more recent investigations, apart from the study of Sorbe *et al.,* the trials of Goldberg *et al.* and Dinniwell *et al.* are also of interest [13, 84, 86]. Goldberg *et al.* examined patients with stage IC-IV OC who had undergone cytoreductive surgery, had received CT, and a part of whom had received consolidation WAI [86]. Median survival in patients with macroscopic disease at second-look laparotomy was 23.5 months if irradiated compared to 18 months if not ($p = 0.05$). Unfortunately, despite the initial survival advantage observed in irradiated patients, owing to late recurrences there was no significant difference in their long-term survival probability. Dinniwell *et al.* assessed the feasibility of WAI following cytoreductive surgery and carboplatin/paclitaxel CT in patients with FIGO stage I-III OC and reported 4-year actuarial DFS and OS of 57% and 92%, respectively [13].

The therapeutic potential of WAI as a salvage therapeutic modality in patients with OC was also a subject of intensive investigation in the late 1990s [87-91]. Ten years later Sedlacek *et al.* performed a study aimed at evaluating the efficacy and safety of WAI as salvage treatment in patients with recurrent epithelial OC who failed aggressive cytoreductive surgery followed by multiple-drug platinum-based CT [53]. Survival rates at years 1 to 5 were 66%, 48%, 26%, 15% and 15% respectively. Residual disease at initiation of radiation correlates strongly with length of survival. The patients with microscopic disease survived an average of 63 months (range 30-111 months). Patients with disease larger than 2 cm survived an average of 9 months (range 5-17 months). This experience strongly suggests that WAI is a viable salvage option, especially for patients with microscopic retroperitoneal disease or small-volume macroscopic disease. In the same year, 1997, similar results – 50% 5-year actuarial disease-specific survival (DSS) in platinum-refractory persistent or recurrent OC with WAI – were established by Cmelak and Kapp [8].

According to most of the authors consolidative and salvage WAI as effective treatment especially in patients with minimal residual disease cannot be and should not be neglected and discarded [8, 13, 83-86, 91, 92].

Palliative whole abdomen irradiation

Palliative RT provides a safe and effective complementary or alternative treatment option for CT-resistant and for recurrent OC. Studies have shown that involved field palliative RT can produce a response rate of 50-80% for symptomatic OC [27, 93-97]. The duration of response has been considered acceptable as most patients have reduced life expectancies after disease recurrence.

Unfortunately, the clinical investigations on the palliative possibilities of WAI are rather scarce. The trial of Faul *et al.,* who studied prospectively the palliative effect of hypofractionated WAI in a small number of patients with chemoresistant OC, is of special interest [39]. All patients had symptomatic and measurable intra-abdominal disease. Patients were treated with a single radiation fraction (7 Gy) or two fractions (3 Gy twice a day) to the abdomen over 1 day. All were heavily pretreated and 9 (56%) had a poor performance status prior to treatment. Symptoms needing palliation included pain (14), ascites (10), and bleeding (2). Symptomatic improvement occurred in all patients with pain (5 complete response rate and 7 partial response), all patients with bleeding, and two (20%) with ascites. Five patients had a reduction in lesion size documented radiologically in three. Median survival was 3 months from the date of treatment. According to the authors hypofractionated palliative WAI is an effective palliative treatment for end-stage OC.

Discussion

Ongoing basic research for better understanding of biological behaviour of epithelial OC and of so far unknown prognostic factors, and persistent efforts for earlier diagnosis of OC, continue to be topical and indispensable issues. Close interdisciplinary cooperation between gynaecologists, radiotherapists and chemotherapists is just as important and proved to be essential for optimum programmes of combined therapy of OC. This is the only way to more effectively control the disease, which still is, diagnostically and therapeutically, one of the major problems in oncogynaecology.

Surgery is considered the mainstay of diagnosis and treatment in early epithelial OC. It is well known that only

accurate staging laparotomy can detect subclinical ovary disease, thus allowing the identification of early tumours. However, the complete macroscopic removal of malignant disease is not synonymous with cure. Many postoperative treatments have been carried out in order to improve the prognosis of patients with OC.

CT is the main and standard adjuvant treatment for OC. The introduction of platinum-containing regimens offered impressive early results even with macroscopic residual disease and made an even stronger case for adjuvant CT. However, the long-term experience proves that although producing a good response rate, platinum-based CT may not improve long-term survival rates over previous treatments [5]. Recently, the combination of paclitaxel and cisplatin became a standard treatment for OC [1-3]. Two large studies in which a combination of cisplatin and taxanes was used showed a significant impact on survival [3, 6]. However, a third and larger study with the same combination of chemotherapeutics showed no improvement at all and both regimens, platinum and taxanes based, were similarly effective [98].

Obviously, if a benefit of CT exists, it is a small one, leaving enough space to explore different approaches. The high recurrence rates of more than 60% at 10 years and the presence of residual disease at second-look laparotomy in approximately half of the patients who appear to be in complete remission post-chemotherapy prompted researchers to consider additional treatment. Some recent clinical trials presented at ASCO 2008 are of interest in this context. An example in this respect is the attempt to study and overcome chemoresistance, which is one of the basic problems in OC treatment. It has been established that elevated levels of the DNA repair protein Breast Cancer 1 (BRCA1) has been associated with platinum resistance, whereas low BRCA1 expression correlates with improved survival in patients with advanced OC [99]. The studies on the therapeutic potential of a novel, potent oral poly ADP-ribose polymerase inhibitor (AZD2281) with single agent anticancer activity in patients with BRCA-deficient OC are also of interest. It is expected that there will be induction of cancer specific synthetic lethality in homologous recombination repair defective cells, including BRCA-deficient tumours [100]. Some authors found that there were no differences in the clinical outcomes when adding oregovomab mono-immunotherapy to the front-line therapy in a selected patient population with OC [101]. Targeting angiogenesis pathways is becoming an important therapeutic option for patients with OC too. Some authors have explored the association between tumour markers of angiogenesis and clinicopathological factors in OC [102]. Other investigations deserving attention are the studies on gene therapy with intraperitoneal EGEN-001, a novel IL-12 gene therapeutic, which demonstrates potential anti-tumour activity, when given alone or in combination with CT in patients with recurrent OC [103].

On the other hand, as early as in the first half of the 20th century, the efficacy of RT as adjuvant WAI, then called "X-ray abdominal bath", in the treatment of OC was well known [104]. Despite the publication of randomized studies reporting 5- and even 10-year survival rates ranging from 45% to 71%, the controversy on the role of WAI continues, mainly because of the restricted size of the studies, the deficient staging of patients, as well as of technical aspects of the RT used [11, 18, 70]. Dembo and his group were the first to show the benefit of RT in a randomized trial, where the WAI gave significantly better 10-year survival compared with pelvic irradiation plus CT [105]. According to the majority of authors WAI has proved to be a safe adjuvant treatment for carefully selected patients with OC, especially in patients who can be or have been debulked to small amounts of residual disease [8, 13, 61, 68, 106]. It offers a localized treatment that has the potential to decrease the risk of abdominal recurrence by 40% [18]. WAI should also be considered in patients who fail initial CT. Its results appear to be as good as or better than second line CT, particularly in platinum-refractory patients [8, 107-111]. Most of the studies have also demonstrated that WAI as a sole adjuvant treatment after surgery or combined with CT is associated with an acceptable rate of acute and late treatment complications [112]. They have also shown that the addition of WAI does not limit the ability of patients to tolerate salvage CT.

Unfortunately, the observed modest results obtained with current CT regimens, as well as the search for new therapeutic approaches, still warrants the development of a large multicentre randomized trial exploring the use of WAI. However, we consider that WAI has been proved to be an effective anti-tumour modality in OC and cannot be discarded with levity. Instead of excluding it entirely from the therapeutic programmes when including treatment approaches with still insufficiently proven possibilities, it is more expedient to seek its optimal implementation as part of the complex therapeutic protocols. It is to be regretted that the inevitable conclusion, which has been drawn for already more than two decades and has not yet found a practical solution, has to be repeated again with respect to the necessity of future studies for determining conclusively which patients are most likely to benefit from the aggressive treatment approach including surgery, CT, innovative techniques of whole abdomen RT and some novel alternative approaches.

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