RESEARCH ARTICLE

Neoadjuvant chemotherapy followed by radiotherapy and concurrent hyperthermia in patients with advanced-stage cervical cancer: A retrospective study

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Abstract
Objective: To evaluate the efficacy of neoadjuvant chemotherapy, followed by radiotherapy and concurrent hyperthermia (triple therapy) in patients with advanced-stage cervical cancer.

Methods: We selected 43 patients from our hyperthermia database, who were treated from 1996 to 2010 with triple therapy for large primary tumours (>6 cm) or para-aortic lymph node metastases. All patients received platinum-based chemotherapy followed by full-dose radiotherapy, brachytherapy and five hyperthermia treatments. The response was evaluated by gynaecological examination and a CT-scan. Time-to-event variables were estimated using the Kaplan Meier method and the Cox regression method.

Results: The mean age of the patients was 50.4 years (range 29–80). The median tumour size was 5.6 cm at diagnosis (range 2.6–8.2), positive lymph nodes were present in 90.7%. A total of 67% of the patients completed all six planned courses of chemotherapy. After completion of neoadjuvant chemotherapy, 83.7% of patients achieved a complete or partial response. At the end of treatment, the complete response rate was 81.4% (95%CI 69.2–93.5). Grade 2, 3 and 4 acute vascular toxicity occurred in 17 patients. The incidence of grade 3–4 haematological toxicity did not exceed 10% and no neutropenic fever occurred. For grade 1–2 renal toxicity, a switch to carboplatin was made (n = 6). No acute grade 3–4 renal toxicity was observed. No treatment-related deaths were recorded. The median follow-up time was 29.8 months (range 4.1–124.8). Overall survival rate at 12 months was 79% (95%CI 57.4–92.3).

Conclusion: The triple therapy seems feasible and effective in the treatment of advanced-stage, high-risk cervical cancer. However, chemotherapy-induced vascular toxicity occurred frequently, which may warrant the use of prophylactic anticoagulants. We recommend a phase II trial for prospective confirmation for comparison with standard chemoradiation and the use of anticoagulants.

Keywords: advanced-stage cervical cancer, neoadjuvant chemotherapy, para-aortic lymph nodes, radiotherapy and hyperthermia

Introduction

Cervical cancer is the second most common cancer in women and is the most prevalent female malignancy [1–3].

For many decades, radiotherapy has been the mainstay of treatment for inoperable cervical cancer, but recurrence rates still range between 41% and 72% [4–6]. Cisplatin is the most commonly used radiosensitiser in the treatment of cervical cancer, and several meta-analyses have shown a significant improvement in local control, progression-free survival (PFS) and overall survival (OS) [7–9]. The combination of hyperthermia and radiotherapy has been shown to be a valuable alternative to chemoradiation for patients with locally advanced cervical cancer. The success rates of concurrent

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chemoradiation with cisplatin and of combining radiotherapy with hyperthermia are comparable, and the efficacy of hyperthermia has especially been demonstrated in patients with large primary tumours [10]. Local control and OS doubled in patients treated with radiotherapy and hyperthermia, without any additional toxicity, compared to radiotherapy alone [11].

However, high local failure rates in patients with large primary tumours (>6 cm) and/or lymph node metastases further stresses the need to improve treatment for these patients. For patients with bulky tumours, treatment outcome of combined radiotherapy and hyperthermia may be improved further when treatment is preceded by neoadjuvant chemotherapy. The same treatment strategy may be beneficial for patients with lymph node metastases. Therefore, since 1996, we have offered patients with locally advanced cervical cancer with either bulky tumours or lymph node metastases to the common iliac or para-aortic lymph nodes, platinum-based chemotherapy followed by extended field radiotherapy combined with locoregional hyperthermia (hereinafter referred to as triple therapy) to maximise these patients’ chances of disease control and cure. In this paper, we report on the OS rate, response rate, acute treatment-related toxicity and local control with this multimodality treatment for patients with advanced cervical cancer and bulky tumours and/or para-aortic lymph node metastases.

**Material and methods**

**Patient selection**

All patients who were treated in the period from August 1996 to January 2010 with neoadjuvant chemotherapy followed by radiotherapy and concurrent hyperthermia for large primary cervical cancer (>6 cm) and/or para-aortic macroscopic lymph node metastases were selected from the hyperthermia database. Routine pre-treatment work-up consisted of gynaecological examination under general anaesthesia, CT scan of the thorax and abdomen or MRI scan. Lymph nodes exceeding 1 cm on a CT or MRI scan assessed by a radiologist, are considered clinically positive. For staging, the International Federation of Gynaecology and Obstetrics (FIGO) system was used.

**Chemotherapy**

All patients were treated with platinum-based chemotherapy in a weekly schedule according to local hospital policy. All patients were examined by a medical oncologist prior to and after every course of chemotherapy. Acute toxicity during chemotherapy was scored using the Common Toxicity Criteria (CTC) version 3.0.

**Radiotherapy**

Two to six weeks after the completion of chemotherapy, patients started their combined treatment of external beam radiotherapy (RT), hyperthermia and brachytherapy. External beam RT was delivered by megavoltage equipment using an equally weighted four-field box technique with 6–10 MV photons to treat the primary tumour, (proximal) vaginal wall, parametria, and draining pelvic lymph nodes. The same technique was applied when the para-aortic region was included up to the level of L2–L3 in case of positive lymph nodes along the common iliac artery. In the case of para-aortic lymph node metastasis, two parallel opposed anterior–posterior fields were used to include the draining lymph nodes up to the level of Th10–Th11. Customised blocks were designed to protect the small bowel, rectum, and caput femoris. In 23–28 daily fractions of 1.8–2.0 Gy, five times a week, a total dose of 46.0–50.4 Gy was delivered to the pelvic structures. The dose to the para-aortic lymph nodes was restricted to 46.0–48.6 Gy. Patients with residual parametrial tumour at the time of first brachytherapy (BCT) usually received an additional pelvic sidewall boost, thus increasing the total dose delivered to the pelvic sidewall to 60 Gy, taking into account the dose contributed by BCT. The BCT was delivered by using 192 Ir (high-dose rate) to a total dose of 17 Gy applied in two fractions, or 18–21 Gy in three fractions; using 137 Cs (medium-dose rate) in a single fraction of 20–24 Gy in 20–24 h or 30 Gy in 60 h (low-dose rate). The BCT technique used depended on availability in the institute in which RT was administered and may have changed during the study period (i.e. some institutes switched from low-dose rate to pulse-dose rate and/or high-dose rate). Dose specifications and homogeneity requirements were according to the International Commission on Radiation Units and Measurements 50 report. Typically, the maximum total dose accepted in critical normal tissue structures considered in treatment planning was 50 Gy for the small bowel, 70 Gy for the rectum and 80 Gy for the bladder. During the period of radiotherapy, patients visited their radiation oncologist weekly for evaluation of acute treatment-related toxicity.

**Deep locoregional hyperthermia**

Patients were scheduled for five weekly hyperthermia sessions during the period of external beam radiotherapy. For all treatments, the BSD-2000 3D system (BSD Medical Systems, Salt Lake City, UT, USA) was used. For thermometry, Bowman
probes were placed intraluminally in the bladder, vagina and rectum with closed-tip catheters. Thermal mapping along the catheters was performed every 5 min with a step size of 1 cm and a maximum map length of 14 cm. Pulse rate and blood pressure were automatically measured before and every 5 min during treatment, and oral temperature was measured at 0, 15, 30, 60 and 90 min. Heating started at a power output of 400 W at 77 MHz. Patients were carefully instructed to report any discomfort due to too high temperatures in normal tissue during treatment. Treatment settings for power, phase and frequency were adjusted accordingly if symptoms developed. If no symptoms developed, 100 W was added to the power output every 5 min. The treatment objective was to achieve intraluminal temperatures of 40–43°C as homogeneously as possible. For all patients, 90-min sessions were scheduled for each hyperthermia treatment; 30 min of heating up and 60 minutes of actual treatment time [12].

Response evaluation

Subsequent gynaecological examinations and general medical examinations were performed after completion of the treatment and during follow-up, in accordance with the guidelines of the Dutch Association of Comprehensive Cancer Centers [13]. Pathological examinations were performed when indicated during follow-up. A CT scan of the thorax and abdomen was made before treatment, after completion of chemotherapy, and after completion of radiotherapy.

For the purpose of this study, all scans were re-evaluated by one of the authors (M.T.) according to the RECIST guidelines version 1.1 [14]. Response after completion of neoadjuvant chemotherapy and radiotherapy was defined as a partial or complete response. A complete response was defined as the disappearance of all visible and palpable lesions, a partial response was defined as at least a 30% decrease in the sum of diameters of target lesions. Responses noted in this study are the best responses achieved for at least 1 month during follow-up. The duration of response was determined from the start of chemotherapy to the date of progression. Follow-up of all patients was done by inquiries at other hospitals and searching our own treatment charts database.

Statistical considerations

Primary end points of this study were OS, PFS and response rate after completion of radiotherapy at 12 months and five years. Acute treatment-related toxicity (grades 3, 4 and 5), age and tumour characteristics on PFS, local control and OS were the secondary end points. The influence of age, tumour diameter, lymph node status, time between primary treatment and recurrence on the OS and PFS were evaluated using the Cox regression analysis. The time-to-event variables were estimated using the Kaplan-Meier analysis and the influence of prognostic factors on the response rate was analysed using logistic regression analysis. P values of less than 0.05 were considered significant. The program used was PASW Statistics 17.0.

Results

Patient characteristics

In total, 43 patients treated with triple therapy for large tumours and/or para-aortic lymph node metastases were identified in the hyperthermia database. Patient characteristics are summarised in Table I. The mean age was 50.4 years (range 29–80). The median tumour size at diagnosis was 5.6 cm (range 2.6–8.2). FIGO stage ≥IIIA was diagnosed in 46.5% (20/43) of the patients. A total of 91% (39/43) of the patients had positive lymph nodes at presentation, of which 77% (33/39) to extrapelvic lymph nodes. The median follow-up time was 29.8 months (range 4.1–124.8).

Table I. Patients characteristics (N = 43).

| Age, years | Median 50.4 (29–80) |
| FIGO stage | |
| IB2 | 6 (14) |
| IIB | 17 (39.5) |
| IIIA | 1 (2.3) |
| IIIB | 10 (23.3) |
| IVA | 9 (20.9) |
| Histological type | |
| Clear cell carcinoma | 1 (2.3) |
| Adenocarcinoma | 3 (6.8) |
| Adenosquamous carcinoma | 2 (4.5) |
| Squamous cell carcinoma | 32 (72.7) |
| Other (unknown) | 5 (11.4) |
| Lymph node status | |
| No suspicious nodes | 4 (9.3) |
| Regional | 6 (14.0) |
| Regional and para-aortic | 28 (65.1) |
| Para-aortic | 3 (7.0) |
| Supraclavicular | 2 (4.7) |
| Tumour size | |
| Median | 5.6 (2.6–8.2) |
| <6 | 15 |
| 6.0–7.0 | 7 |
| >7.0 | 4 |

Treatment characteristics and adverse events

Of all patients, 40 completed extended field radiotherapy and BCT after neoadjuvant chemotherapy,
and 40 completed three to five hyperthermia sessions. All patients were eligible for toxicity evaluation (Table III). No treatment-related deaths were recorded.

Chemotherapy

All patients received platinum-based chemotherapy as part of a multi-drug regimen. The precise schedule depended on local hospital policy and patient comorbidity and is summarised in Table II. A total of 36 patients received cisplatin combined with paclitaxel \((n = 25)\) or etoposide \((n = 8)\), or as part of the MVAC regimen (methotrexate, vinblastine, doxorubicin and cisplatin) \((n = 3)\). Others received carboplatin combined with paclitaxel \((n = 6)\) or 5-FU \((n = 3)\). A total of 73% \((29/40)\) of the patients completed all six planned courses of chemotherapy. Three patients completed all three planned courses of the MVAC regimen. Eleven patients stopped chemotherapy due to reasons of toxicity such as renal toxicity, ototoxicity and coronary spasm. Six of eleven patients changed from cisplatin to carboplatin-based chemotherapy due to renal toxicity.

Complete toxicity data of chemotherapy were available for 34 patients; for 9 patients treated with chemotherapy, the clinical toxicity data or laboratory data were incomplete. As summarised in Table III, the most common adverse events of neoadjuvant chemotherapy were haematological toxicity, nausea, vomiting and alopecia, and most were grades 1–2. Grade 3 nausea, vomiting and anorexia were observed in two patients. Grade 3–4 leukopenia and neutropenia were observed in 7% \((3/43)\) and 9% \((4/43)\) respectively. Grade 3 thrombocytopenia was observed in one patient. Neutropenic fever was not observed. Grade 3–4 non-haematological toxicity consisting of vascular toxicity was observed in 16 patients. Thromboembolic events occurred in 17 of 43 patients \((39.5\%)\), see Table IV, such as symptomatic pulmonary embolism \((n = 6)\), deep venous thrombosis \((n = 5)\), thrombotic stenosis of the aorta \((n = 2)\), cerebrovascular accidents \((n = 2)\), symptomatic intracerebral sinus thrombosis \((n = 1)\), and transient ischaemia of the arm \((n = 1)\). All patients were treated with a low molecular weight heparin (LMWH) and recovered without any residual symptoms. One patient suffered from late severe renal toxicity \((grade 2)\), who recovered to a calculated creatinine clearance level of 30 mL/min.

Radiotherapy and hyperthermia

All patients completed the radiotherapy treatments as prescribed. In 33 patients, irradiation of the para-
aortic lymph nodes was indicated and they received a total dose of 48.6 Gy to the pelvis and the para-aortic lymph nodes. In ten patients, irradiation of the para-aortic lymph nodes was not indicated and they received 46–50 Gy to the pelvis only. Eleven patients received an external boost (range 10–24 Gy) on the local tumour \( (n = 3) \) or the iliacal lymph node mass \( (n = 8) \).

A total of 40 patients underwent brachytherapy. Three patients did not receive brachytherapy due to insufficient tumour regression or fear of perforation during the procedure. Thirty-five patients completed all five hyperthermia treatments, eight patients stopped hyperthermia because of severe discomfort or intolerance (see Table II). During combined radiotherapy and hyperthermia, grade 3–4 acute toxicity did not occur. One patient developed hyperthermia-related acute toxicity, i.e., a subcutaneous burn to the pelvic area that healed without further medical attention. Late radiotherapy-related toxic events occurred in at least three patients and consisted of proctitis \( (n = 2) \) and cystitis \( (n = 1) \).

Response rate and survival

In Table IV, the response rates after neoadjuvant chemotherapy and after completion of the radiotherapy treatment are reported. After completion of neoadjuvant chemotherapy, 83.7% of patients achieved a complete or partial response. At the end of the treatment, the complete response rate was 81.4% \( (95\% \text{CI} 69.2–93.5) \). During follow-up, 18 out of 43 patients died, because of progression or non-tumour related death, and in 24 patients local progression was reported. Local regional failure of tumour control, and distant metastasis occurred in 15 patients, six patients had only distant failure, and three patients had local regional failure. Six of these patients were still alive on September 2011. OS was 79% \( (95\% \text{CI} 57.4–92.3) \) at 12 months, whereas the 5-year OS rate was 55% (Figure 1). Local control was obtained at the end of treatment in 40 patients. Local control was 43% at 5 years \( (95\% \text{CI} 35.2–64.9) \) (Figure 2). PFS rate at 12 months was 66% \( (95\% \text{CI} 44.6–81.3) \) (Figure 3), whereas the PFS rate at 5 years was 45%. Logistic regression analysis showed that age had no significant influence on complete response rate \( (p = 0.352) \). Also, neither FIGO stage nor lymph node status had a significant influence on the complete response rate with \( p \) values of 0.09 and 0.939, respectively. Cox regression analysis was performed on local control: FIGO stage, lymph node status and age were all of no significant influence.

Finally, Cox regression analysis also showed that FIGO stage, lymph node status and age had no significant influence on OS with \( p \) values of 0.211, 0.555 and 0.073 respectively.

Discussion

The present study was designed to determine the effects of treatment with neoadjuvant chemotherapy
followed by subsequent radiotherapy and hyperthermia (triple therapy) in locally advanced cervical cancer with or without positive lymph nodes. The results of our study show that in this difficult-to-treat patient group, a complete response after ending treatment was achieved in 81.4% of the patients, OS was 79%, and PFS was 66% at 12 months. Local tumour control was 43% at 5 years and OS rate was 55% at 5 years. Median follow-up time was 29.8 months, the broad range in follow-up time is due to one patient with progressive disease after ending treatment, and on the other hand prolonged survival of a patient treated at the beginning of the study. A striking finding was the high incidence of grade 3–4 vascular toxicity, which occurred in 39.5% of the patients during neoadjuvant chemotherapy.

Reports on the treatment outcome of chemoradiation and toxicity for these specific subgroups of cervical cancer patients (locally advanced cervical cancer with or without positive lymph nodes or bulky tumours) are scarce, making a comparison to other types of treatment difficult. Survival of patients with para-aortic lymph node metastases at the time of the initial diagnosis is poor. Most reports of radiation therapy alone for patients with biopsy-proven para-aortic lymph node metastases describe a median survival rate of about 2 years and a 5-year survival rate of 32% [15]. In most randomised trials, patients with lymph node metastases were excluded, so the value of this treatment approach for this unfavourable subgroup of cervical cancer patients remains unsure [16].

The failure of radiotherapy to control large pelvic tumours may be related to the relative resistance to radiotherapy of hypoxic cells within a large tumour mass. In 2001 a systematic review and meta-analysis of available published and unpublished summary data from 19 randomised trials, comparing concomitant chemoradiation versus radiotherapy, showed a 29% reduction in the risk of death, which translated in an OS benefit of 12% at 5 years for concomitant chemoradiation. Since then chemoradiation has become the standard treatment approach for locally advanced cervical cancer, irrespective of the stage or pelvic lymph node involvement [17–18]. However, the benefit of chemoradiation is far less obvious for the more advanced stages of cervical cancer.

Since 1990, hyperthermia in combination with radiotherapy has been used in the treatment of advanced stage cervical cancer, and in the Netherlands it has been recommended for patients with a medical contraindication for chemoradiation [19]. An update of the Dutch Deep Hyperthermia Trial (DDHT) in patients with cervical cancer showed that long-term follow-up in the DDHT sustained improvement in local control and overall survival after 12 years by combining radiotherapy and hyperthermia. In this trial, patients had large and advanced tumours but in most of these patients the lymph node status was unknown or they were not proven lymph node positive [11]. Patients with locally advanced tumours are expected to benefit less from concomitant chemoradiation, and may benefit more from the addition of hyperthermia to radiotherapy, because hyperthermia may increase sensitivity of the tumour to radiotherapy [10–11, 20] as well as decrease the hypoxic cell fraction in a tumour.

The use of neoadjuvant chemotherapy in this specific subgroup may also be beneficial by means of reducing the tumour load before the start of definitive radiotherapy and may thus improve the overall response.

Neoadjuvant chemotherapy for patients with cervical cancer has been the subject of debate for years. A large Cochrane meta-analysis of more than 3000 women failed to detect a statistically significant beneficial effect of neoadjuvant chemotherapy [2]. However, the systematic review and meta-analyses of individual patient data from 21 randomised trials on neoadjuvant chemotherapy followed by radical radiotherapy, compared to the same radiotherapy alone, showed a high level of statistical heterogeneity. Trials using short chemotherapy dose intervals, or cisplatin dose intensities greater than or equal to 25 mg/m² per week, tended to show an advantage for neoadjuvant chemotherapy on survival. In contrast, trials using longer dose intervals or lower cisplatin dose intensities tended to show a detrimental effect of neoadjuvant chemotherapy. Thus, the timing and dose intensity of cisplatin-based neoadjuvant chemotherapy appeared to have an important impact on the success and failure [21]. We treated our patients with a high dose of cisplatin of 70 mg/m² once weekly for six courses, which is a relatively high-dose intense chemotherapy. Several papers have been written on neoadjuvant chemotherapy followed by either chemoradiation or surgery. Firstly, it is unclear if it can be expected that in a pretreated tumour concurrent chemotherapy still acts as a radiosensitiser; secondly, cumulative toxicity especially due to cisplatin-based chemotherapy can be expected. This favours the use of concurrent hyperthermia and radiotherapy, as it also works synergistically. Since treatment-related toxicity is increased when chemotherapy is combined with pelvic field radiotherapy for patients with extrapelvic lymph node metastases, many institutes are reluctant to combine extended field radiotherapy with cisplatin, as this may lead to unacceptable toxicity in view of the large radiation fields. The second advantage of hyperthermia–radiotherapy over chemoradiation is that extended field radiotherapy can be offered without significantly increased
Several mechanisms are thought to contribute to the hypercoagulable state of cancer patients treated with chemotherapy. In 2005, Jacobson et al. found a 16.7\% incidence of thromboembolic events in patients with cervical cancer treated with cisplatin-based chemoradiation Alterations in coagulation factors, anticoagulant proteins, and endothelial cell alteration or injury all seemed to be associated with the development of thromboembolic events [25]. In search of prevention of vascular events, Lin et al. reported in 2006 in a study in patients with cervical or vulvo-vaginal cancer treated with chemoradiation that the use of warfarin had no effect on the incidence of deep venous thrombosis [26]. On the other hand, in 2003 Lee et al. compared the use of a low-molecular-weight heparin (LMWH) in 336 patients in both groups with a coumarin in the prevention of recurrent venous thromboembolism in cancer patients. In this study, the use of a LMWH, 27 versus 53 in the coumarin group, was more effective in reducing the risk of recurrent thromboembolism without an increased risk of bleeding [27].

**Conclusion**

This study reports on treatment results of this novel approach of neoadjuvant chemotherapy followed by concurrent radiotherapy and hyperthermia in a difficult-to-treat patient group with large primary tumours, the vast majority of whom also had para-aortic lymph node metastases. The triple therapy seems feasible in the treatment of advanced-stage high-risk cervical cancer although a high incidence of vascular toxicity after chemotherapy was found. It is very important that this multimodality treatment is investigated more thoroughly, as the potential benefits, improved PFS and OS need to outweigh the potential hazards. In this study, vascular toxicity during treatment with chemotherapy occurred frequently, which may warrant prophylactic use of anticoagulants. We recommend a phase II trial for prospective confirmation for comparison with chemoradiation and the use of LMWH. We recommend a prospective phase II trial for comparison of standard chemoradiation with neoadjuvant or adjuvant chemotherapy followed by radiotherapy and hyperthermia with or without LMWH for patients with locally advanced-stage cervical cancer.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
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