



Post-operative radiotherapy in patients with early stage cervical cancer



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HIGHLIGHTS

- Between 1970 and 1990, both tumour recurrence and mortality showed a remarkable decrease.
- The major associated change in treatment policy was addition of a local vaginal vault brachytherapy boost.
- Chemotherapy did not have a major impact on survival, but did increase toxicity.

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ABSTRACT

Objective. The aim of this study is to investigate the impact of treatment policy changes in cervical cancer patients treated with adjuvant (chemo) radiotherapy.

Methods. Between 1970 and 2007, 292 patients received adjuvant radiotherapy after a radical hysterectomy with pelvic lymphadenectomy for early stage cervical carcinoma. All patients received pelvic radiotherapy (40 Gy–46 Gy in 1.8 Gy–2 Gy/fraction). Vaginal vault brachytherapy boost (10–14 Gy) was increasingly used for patients with high-risk factors, and since 1993 systematically applied in patients with at least 2 of the 3 risk factors: adenocarcinoma, nodal involvement and parametrial invasion. Cisplatin-based chemotherapy was introduced in this group of patients from 2000.

Results. The 5-year cumulative risk of local recurrence (CRLR) was 13% (95%CI 9%–17%), resulting in an overall 5-year survival (OS) of 78% (95%CI 83%–73%). Since 1970, the OR for the 5-year locoregional recurrence risk (LRR) decreased from 2.5 to 1.15 (linear-OR = –0.02/year). The OR for the 5-year mortality risk reduced from 2.2 in 1970 to 1.0 in 2007 (linear-OR = –0.03/year). The largest risk reductions were observed before 1990 with a minor rise after 2002. The risk of severe late toxicity reduced from 1.8% to 1.5% (linear-OR = –0.03/year). The addition of concomitant adjuvant chemotherapy since 2000 may have benefited a subgroup of patients with squamous cell carcinoma, but not the patients with adenocarcinoma, and after introduction of chemotherapy the risk of severe late toxicity tripled from 2% to 7%.

Conclusion. Since 1970, tumour recurrence risk and mortality have decreased, as radiation dose increased. The potential benefit of concomitant adjuvant chemotherapy could not be demonstrated in this nonrandomized study.

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Introduction

Cancer of the uterine cervix is the second most common cancer among women worldwide, although it is much more common in developing countries than in western societies [1]. In 2011 in The Netherlands, about 749 women were diagnosed with cervical cancer and 189 died from cervical cancer, with a European world-age

standardized incidence and mortality rate (ESR) of 7.93 and 1.68, per 10⁵ person per year respectively [2,3].

Early stage cervical cancer can be primarily treated with either radical surgery or radiotherapy. Similar results have been reported in terms of overall and disease-free survival, although different patterns of toxicity are described [4–6].

Various prognostic factors have been recognized. Patient related factors include tumour stage, depth of stromal invasion, parametrial invasion, lymphovascular space invasion, presence of lymph node metastasis and histological type [5,7–10].

In the Dutch national guidelines, post-operative radiotherapy (PORT) is indicated in case of positive surgical margins, invasion of lymph nodes or in case of parametrial invasion [11–14].

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The indication in case of other poor prognostic factors such as capillary space involvement, tumour size of 4 cm or more, deep stromal invasion (more than one third) and adeno- or adenosquamous histology has been a matter of debate for a long period [8,10,13,15,16].

The updated analysis of Gynaecologic Oncology Group study 92 showed that pelvic radiotherapy after radical surgery significantly increased the progression free survival in patients with stage IB cervical cancer with negative lymph nodes, and 2 or more of the following features: deep stromal invasion, capillary space involvement, and tumour diameter of more than 4 cm [17].

The indications for chemotherapy in combination with surgery, radiotherapy or both modalities in high-risk early stage patients became evident in 1999, and it was later confirmed in different studies and a meta-analysis [5,18–20].

In our clinic, surgery is the first-choice treatment in patients with early cervical cancer, unless a patient is medically unfit for surgery or in elderly patients (>70 years) [21,22]. PORT is routinely performed in case of lymph node metastasis, parametrial invasion, positive surgical margins or intraoperative spill [23].

In the mid-nineties, the data on the outcome of treatment of early cervical cancer patients treated in our centre with PORT from 1970 to 1993 were analysed. This analysis revealed the poor prognosis of patients with both lymph node metastasis and parametrial invasion or one of these factors in patients with an adenocarcinoma [14,24]. As a result, the treatment policy in our centre was adapted in 1994 and brachytherapy to the vaginal vault was systematically administered in these patients. From 2000 onwards, these patients received concomitant cisplatin with post-operative radiotherapy.

The present analysis is based on patient data from 1970 to 2007, treated with radical hysterectomy and PORT for early stage cervical cancer. The purpose was to investigate the impact of treatment policy changes over the time in terms of OS, LC, distant recurrence (DR) and treatment complications, and to analyse the influence of different prognostic factors.

Materials and methods

Patient characteristics

Between 1970 and 2007, 292 patients diagnosed with early stage cervical carcinoma received post-operative radiotherapy (PORT) after a radical hysterectomy and pelvic lymphadenectomy (RHPL); 102 had an abdominal vaginal radical hysterectomy and lymphadenectomy (AVRUEL) and 190 had a Wertheim–Okabayashi procedure. All patients were discussed in a multidisciplinary tumour board. Indications for PORT varied according to the treatment period. From 1970 to 1993, patients with one or more lymph node metastasis in the operative specimen, parametrial invasion or in whom the resection margin was not radical, were systematically treated with adjuvant external beam radiotherapy, with or without brachytherapy.

Since 1994, brachytherapy to the vaginal vault was systematically given in cases of histology of adenocarcinoma and/or the presence of both lymph nodes metastasis and parametrial invasion. Concurrent chemotherapy was given from 2000 to these patients as well. Not included in this analysis were patients with small cell type tumours, those in whom the indication of PORT could not be documented, and patients whose follow-up was missing.

Fig. 1 gives an overview of treatment changes, and variation in some patient and tumour characteristics along the study period. Patient and tumour characteristics are shown in Table 1a.

All the data were prospectively entered in a database from 1993 onwards.

Treatment modifications over time

Surgery consisted of a RHPL. From 1970 to 1981, the AVRUEL procedure, a combined abdominal and vaginal approach, was performed [21].

In 1982 the Wertheim–Okabayashi technique was gradually introduced [22,25].

Radiotherapy was given to the pelvis, the upper limit being placed at the intervertebral level between L4 and L5, and the inferior limit at the inferior border of the pubic bone. Before 1979, the superior border was at the level of the inferior border of L5 in selected patients. Lateral margins were 2 cm lateral of the bony rim of the pelvic wall. Megavoltage therapy was applied in all patients. Since then, the AP/PA technique was replaced by a 4-field conformal box technique, the lateral fields were in general 9 cm wide, with a posterior limit situated at the intersection of S2/3. The dose varied between 40 and 50.4 Gy in fractions of 1.8–2 Gy and it was recalculated to a biological equivalent EQD2 of 2 Gy per fraction ($\alpha/\beta = 10$ for tumour) [26]. Para aortic fields were used in case of the presence of metastasis situated at the level of the common iliac vessels or higher. From 1994, a belly board was introduced enabling a better bowel sparing radiation technique.

Brachytherapy was given to the vaginal vault with various techniques within this period. If radium (Ra eq) was used, a dose of 1500 mgh was administered at 5 mm depth from the mucosa surface; this area was blocked from external therapy for 20 Gy. After the introduction of a low dose rate (LDR) after-loading technique (Selectron) in 1980, a dose of 10 Gy was prescribed at 5 mm depth from the mucosa surface using a Cesium-137 source. From 2004 onwards, the patients were treated with a pulsed dose rate (PDR) after-loading device with Iridium-192 source.

Chemotherapy consisted of cisplatin 40 mg/m² once a week during the weeks of external beam radiotherapy, with a final course the day before brachytherapy. Supportive care included hydration and antiemetics, but no hematopoietic growth factors. During chemoradiation, Hb was maintained at a minimum of 7.5 mmol/L, usually with red cell transfusions, although erythropoietin was allowed.

Treatment characteristics are summarized in Table 1b.

Late toxicity in the period before 1993 was scored according to CTC 2.0 and converted to CTC 3.0. Late toxicity after 1993 was scored according to the EORTC/RTOG criteria (CTC 3.0) [27]. From 1970 to 1993, late complications grade 1 or 2 were unfortunately not properly scored. Hundred and four patients of this period were not included in the analysis of grade 1 or 2 complications because of underscoring.

Follow-up extended from 2.5 to 307 months, with a mean of 80 and a median of 66 months.

Statistical analysis

The vital status of all patients was verified in the Dutch Central Population Register (CBR-Centrale Bevolkings Register) and updated until March 15th, 2013.

Survival was calculated from the date of surgery until death or until March 15th, 2013. The survival curves were constructed according to the Kaplan–Meier method. The influence of patient, tumour and treatment characteristics were analysed using univariate and multivariate Cox regression analysis, using the Breslow method (statistical analysis was carried out with the statistical program R, version 2.13.0). The spline and predict method for generalized linear model fits in R was used to estimate the odd ratios of age or treatment period for the risk of survival, recurrence and metastasis [28].

Loco regional recurrence was defined as tumour recurrence within the radiation fields.

Distant recurrence was defined as any recurrence outside of the radiation portals.

To compare the observed Kaplan–Meier survival with the expected survival in the Dutch elderly female population we calculated an individually matched ‘population survival’ using life tables from Dutch vital statistics for females and for year of diagnosis, the latter to correct for the fact that the Dutch female life expectancy has also improved between 1970 and 2007 [29]. These calculations were performed using the Ederer and Heise method (a.k.a. Ederer II) as implemented in the RELSURV package in the statistical program R [30,31].

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