Pergamon

European Journal of Cancer, Vol. 34, No. 4, pp. 586–590, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10087-9

Short Communication

Postoperative Radiotherapy for Endometrial Carcinoma Stage I. Wide Variation in Referral Patterns but no Effect on Long-term Survival in a Retrospective Study in the Southeast Netherlands

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The aim of this study was to assess the referral pattern and the impact on long-term survival of postoperative radiotherapy in patients with adenocarcinoma of the endometrium stage I. This was a retrospective study performed in a regional cancer registry which covers a population of approximately 1 000 000 persons. All 724 patients registered between 1975 and 1992 in the Comprehensive Cancer Centre South, Eastern Section, The Netherlands, were analysed. All patients had received surgery as primary treatment which was performed in one of the seven community hospitals of the region. Radiotherapy was given in one regional department. All pathology reports were checked for data on tumour differentiation and myometrial invasion. Almost half the patients (45%) were referred for postoperative radiotherapy. The depth of myometrial invasion and the degree of tumour differentiation were the main factors ($P < 0.0001$) influencing referral for postoperative radiotherapy. The referral pattern varied between the different hospitals, but became more similar during 1985–1988, to diverge again in recent years. In patients younger than 60 years, the depth of myometrial invasion was significantly ($P = 0.01$) correlated with survival. In patients older than 60 years, tumour differentiation ($P = 0.05$) and age ($P < 0.001$) were correlated with survival, but not the depth of myometrial invasion. After adjustment for known prognostic factors, a survival benefit of postoperative radiotherapy could not be established. The studied group had an excess death rate over the normal Dutch female population. This excess death rate did not decrease during follow-up, as even after 10 years an excess death rate was found. A prospective randomised trial is ongoing in The Netherlands. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: postoperative radiotherapy, endometrial carcinoma (stage I), referral patterns, survival
Eur J Cancer, Vol. 34, No. 4, pp. 586–590, 1998

INTRODUCTION

ADENOCARCINOMA OF the endometrium is the most frequent gynaecological malignancy, but it also has the lowest associated mortality [1, 2]. Possible reasons for this low mortality rate are early detection, a favourable natural history, and well developed therapies. Surgery is the mainstay of treatment, and often postoperative radiotherapy is given. In 1989 and 1990, two retrospective studies [3, 4] were performed in The Netherlands concerning the value of postoperative radiotherapy. Both studies showed that patients with endometrial carcinoma receiving postoperative radiotherapy had an excellent prognosis, but a control group of patients without postoperative radiotherapy was lacking. As it was not clear if the excellent prognosis was due to the postoperative radiotherapy, or due to the inherent good prognosis of endometrial carcinoma, a prospective randomised trial was initiated in 1990. In the meantime, we started this retrospective study

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Received 9 May 1997; revised 26 Sep. 1997; accepted 23 Oct. 1997.

since, due to the good prognosis, it would take a long time before the results of this trial would be available. Secondly, we hoped to raise interest for the trial. The referral pattern for postoperative radiotherapy in the period 1975–1992 in the Comprehensive Cancer Centre South (CCCS), Eastern section, Eindhoven was studied. This registry is population based and reliable since the 1970s, covering more than 99% of cancer cases [5]. It has a population of approximately 1 000 000 persons. Few patients are referred for treatment outside the CCCS. Originally, surgery was performed in 10 hospitals, but through a merging process there are now seven general hospitals. Postoperative radiotherapy for endometrial carcinoma was given according to informal guidelines based on a periodic decentral consultants system with radiotherapists being senior visiting consultants in all referring hospitals. Radiotherapy was performed in one large regional department, which is part of a general hospital. The maximal distance between the referring hospitals and the radiotherapy department was 50 km.

MATERIALS AND METHODS

The study was limited to patients with postoperative stage I endometrial carcinoma and focused on factors influencing referral for postoperative radiotherapy, while the impact on survival of postoperative radiotherapy and other prognostic factors was also investigated. The CCCS registers all new patients with cancer after notification by pathological laboratories and medical record administration.

All 724 patients registered between January 1975 and December 1992 were analysed. The vital status was actively checked by 1 April 1994, so the minimal follow-up was 1.5 years. The date of arrival for surgical intervention was used as the date of incidence. Tumour stage, tumour differentiation and the depth of myometrial invasion were retrospectively recorded on the basis of the original pathological reports by one of the authors. For tumour stage, the International Union against Cancer (UICC) classification dating from 1971 was used [6]. Tumour differentiation was specified as being well (G1), moderately (G2) or poorly (G3) differentiated. Tumours were classified as being superficially invasive if the myometrium was invaded less than half of its thickness; deeply invasive if the myometrium was invaded equal or more than half of its thickness.

Standard surgical intervention was a total abdominal hysterectomy with ovariectomy, but without lymphadenectomy. Patients were referred for radiotherapy at the discretion of the gynaecologist. In the period studied, there were approximately 20 gynaecologists in the region, one per 25 000 women.

The radiation treatment policy, already described in a previous study [3], consisted of brachytherapy for well differentiated, superficially infiltrating tumours. A dose of 35 Gy in seven fractions of 5.0 Gy, given at a rate of two fractions per week, was given to the vaginal vault. All other patients received external pelvic irradiation to a dose of 40 Gy given by means of a four field technique, all fields being treated daily, five fractions per week. In addition, vaginal vault irradiation was given, dose 20 Gy in four fractions of 5.0 Gy. Adjuvant hormonal treatment was not routinely given.

Statistical methods

Demographic data were obtained from the CCCS, Eastern Section, Eindhoven. Survival was calculated from the date of conclusive histological diagnosis to the date of death, or 1 April 1994 if that was later. Overall survival probabilities were calculated by the method of Kaplan and Meier [7]. The proportional hazard model of Cox [8] was used for multivariate analysis of prognostic factors.

The subject year method was used to calculate the expected number of deaths and expected survival rates from the Dutch female population age specific death rates and the number of years of follow-up in our study. The calculations were adjusted for the change in age distribution of the population at risk during the study. The relative survival rate was calculated as the ratio of the actuarial overall survival probability and the expected survival rate [9]. Standardised mortality ratios were calculated as the ratio between the observed and expected number of deaths. The excess death rates were calculated as the difference between observed and expected numbers of deaths per 100 000 life-years.

RESULTS

Relationship between tumour characteristics and referral for radiotherapy

Of the total of 724 patients, only 324 (45%) had been referred for postoperative radiotherapy. The patient characteristics, referral pattern for radiotherapy and 10-year survival rates (overall and relative) are shown in Table 1. Patients without information about tumour differentiation or myometrial invasion are omitted from the tables. The mean age of the irradiated and non-irradiated patients was similar, 62.0

Table 1. *Patient characteristics, referral for radiotherapy and* 10-*year survival rates*

	Total *n*	RT *n* (%)	10-year survival rates* Overall (%)	10-year survival rates* Relative (%)
Total	724	326 (45)	71 ± 2	87
Age (years)				
< 50	100	36 (36)	87 ± 4	90
50–60	238	100 (42)	84 ± 3	91
60–70	224	123 (55)	73 ± 4	88
> 70	162	65 (40)	39 ± 5	84
Differentiation				
G1	284	85 (30)	81 ± 3	97
G2	319	185 (58)	65 ± 3	82
G3	63	37 (59)	57 ± 8	71
Unknown	58	19 (33)	71 ± 7	84
Myometrial invasion				
< half	428	137 (32)	78 ± 3	93
≥ half	263	174 (66)	63 ± 4	82
Unknown	33	12 (36)	62 ± 10	73
Period				
1975–1979	137	69 (50)	75 ± 4	90
1980–1984	204	108 (53)	70 ± 3	86
1985–1988	192	75 (39)	74 ± 4	87
1989–1992	191	73 (38)	(83 ± 4)†	(91)†
Hospital				
A	69	23 (33)	74 ± 7	85
B	146	69 (47)	70 ± 4	86
C	115	56 (49)	64 ± 6	80
D	117	30 (26)	77 ± 4	95
E	132	75 (57)	68 ± 5	84
F	106	47 (44)	76 ± 5	88
G	39	24 (62)	74 ± 8	109

*Survival probability ± SEM. †Five-year probability.

years versus 62.4 years. Referral rates for radiotherapy were lower for the following categories: patients younger than 60 years, and older than 70 years, G1 tumours, superficially infiltrating tumours and patients diagnosed in later periods. A wide variation in referral was observed between the different hospitals.

Myometrial invasion and tumour differentiation. An important determinant for referral was the depth of myometrial invasion, taking into account age and tumour differentiation (Table 2). Regardless of age and tumour differentiation, patients with deeply infiltrating tumours were more often referred for radiotherapy.

Deep infiltrating tumours were more often seen in patients older than 60 years (51%) than in patients younger than 60 years (23%), explaining the higher referral percentage in patients aged 60–70 years. Patients older than 70 years were statistically significantly ($P < 0.0001$) less frequently referred, even in the presence of deep myometrial invasion. Patients with G2 and G3 tumours were also more frequently referred. A multiple logistic regression analysis showed that referral for radiotherapy was associated with deep myometrial invasion ($P < 0.0001$) and G2 or G3 tumours ($P < 0.0001$).

Referral pattern in time. The sub-periods 1975–1979, 1980–1984, 1985–1988 and 1989–1992 were chosen and age, depth of myometrial invasion, tumour differentiation and whether radiotherapy was given were examined. In the period 1975–1979 the patient population was slightly younger (60.6 years) than in later periods (62.5 years), $P = 0.04$. There was a shift in tumour differentiation, as in the period 1975–1979 markedly more G1 tumours were diagnosed (71%) than in later periods (39%), while the G2 tumours proportionally increased. The G3 tumours slightly increased from 9% in 1975–1979 to 14% in 1989–1992. The distribution according to the depth of myometrial invasion remained stable. The referral percentages between the subsequent periods (Table 1) were different, even after correction for differences in patient population. After 1984, the number of patients referred for radiotherapy declined sharply ($P < 0.0001$). The referral percentage for patients with superficially invasive G1 tumours declined from 34 to 7%, while the referral percentage for patients with G2 G3 tumours and deeply invasive tumours remained stable.

Table 2. Referral for radiotherapy in relation to myometrial invasion, age and tumour differentiation

	Depth of infiltration			
	< Half		≥ Half	
	n	*n* (%) RT	*n*	*n* (%) RT
Total	428	137 (32%)	263	174 (66%)
Age (years)				
< 50	70	21 (30%)	22	14 (64%)
50–60	174	57 (33%)	52	37 (71%)
60–70	114	44 (39%)	104	76 (73%)
> 70	70	15 (21%)	85	47 (55%)
Tumour differentiation				
G1	222	47 (21%)	57	35 (61%)
G2	151	72 (48%)	164	108 (66%)
G3	31	12 (39%)	29	23 (79%)

RT, radiotherapy.

Referral pattern of the different hospitals. The distribution of patient and tumour characteristics according to the different hospitals was comparable with regard to age (median age 62 years, range of medians over hospitals 58–63 years) and the depth of myometrial invasion (> half: mean 38%, range 34–42%). However, with respect to tumour differentiation, a difference was found which was statistically significant ($P = 0.0001$) (G1: mean 43%, range 24–56%; G2: mean 48%, range 26–72%; G3: mean 9%, range 0–19%). After adjustment, the differences in referral for radiotherapy between the hospitals remained statistically significant ($P < 0.0001$). The referral pattern varied between hospitals, and in some hospitals referral for postoperative radiotherapy increased, while in other hospitals it remained stable or even decreased.

Prognostic factors and survival

The following factors were analysed for their association with survival in the Cox regression analysis: age, tumour differentiation, depth of myometrial invasion, period of diagnosis, hospital and whether postoperative radiotherapy was given or not. Age, depth of myometrial invasion and tumour differentiation turned out to be strongly associated with survival, while no trend was observed with period of diagnosis, referring hospital ($P = 0.95$) or whether postoperative radiotherapy was given or not.

The main results concerning relative death rate, confidence intervals and corresponding *P* value are presented in Table 3. The unfavourable impact of deep myometrial invasion was restricted to the younger patients, while the impact of tumour differentiation was restricted to the older patients. The depth of myometrial invasion was associated, both with tumour differentiation (48% of the G3 patients had deep myometrial invasion versus 20% of the G1 patients), and with age (23% of the patients younger than 60 years had deep myometrial invasion versus 51% of the patients older than 60 years). Tumour differentiation was weakly associated with age ($P = 0.07$, details not shown). After adjustment for known prognostic factors, an effect of postoperative radiotherapy was not found in either of the age groups.

Table 3. Cox regression analysis

	RR (95% CI)	*P* value
Age ≤ 60 years		
Tumour differentation		0.88
G2 versus G1	0.84 (0.4, 1.7)	
G3 versus G1	0.94 (0.3, 2.7)	
Depth of infiltration		0.01
≥ half versus < half	2.47 (1.2, 4.9)	
Age (years)	1.03 (0.97, 1.09)	0.33
Radiotherapy		
Yes versus No	1.06 (0.6, 2.0)	0.86
Age > 60 years		
Tumour differentation		0.05
G2 versus G1	1.45 (0.98, 2.2)	
G3 versus G1	1.96 (1.1, 3.5)	
Depth of infiltration		0.88
≥ half versus < half	0.97 (0.7, 1.4)	
Age (years)	1.08 (1.06, 1.11)	< 0.0001
Radiotherapy		
Yes versus No	0.99 (0.7, 1.4)	0.95

RR, relative death rate; CI, confidence interval.

The results of the Cox regression analysis were in agreement with a comparison of observed and expected mortality rates in different subgroups. Of the 724 patients, 193 have died, compared with an expected number of 110. This corresponds with an excess death rate of 1.6 per 1000 person-years. The excess death rate did not decrease with longer follow-up. Of the patients with a follow-up longer than 10 years, 33 have died compared with an expected number of 22, corresponding to an excess death rate of 1.5. The relative 10-year survival rate was 87% (Table 1). Relative survival decreased from 90% for patients below the age of 60 years to 84% for patients over the age of 70 years. Patients with deep invasive tumours had a lower relative 10-year survival rate than patients with superficial infiltrating tumours (82% versus 93%). The 10-year relative survival rate decreased from 97% for patients with G1 tumours to 71% for patients with G3 tumours. The association between relative survival and tumour grade was most prominent among the patients older than 60 years: a 10-year relative survival rate of 100% for patients with G1 tumours versus 59% for patients with G3 tumours.

DISCUSSION

This study showed that in the period 1974–1992, only 45% of the patients undergoing a hysterectomy for adenocarcinoma of the endometrium were referred for postoperative radiotherapy. All patients should have been referred for radiotherapy if the gynaecologists had adhered to the guidelines of the regional radiotherapy department. The indications for postoperative radiotherapy of stage I tumours were as follows: patients with G1 and superficially invasive tumours, only brachytherapy and a combination of pelvic irradiation and brachytherapy for all other patients.

Referral was significantly associated with depth of myometrial invasion and tumour differentiation, but this could not explain the wide variation in referral pattern. A disturbing factor is hospital merging resulting in currently seven community hospitals instead of 10 community hospitals in 1975. Nevertheless, the observed differences in referral pattern between hospitals were substantial, although the patient populations differed only in respect of tumour differentiation. Moreover, the referral pattern changed in time but in a different way in the different hospitals. After 1984 an important decrease in the overall number of patients referred for radiotherapy was observed.

A clear explanation for this observation is not available, although one of the possibilities is the influx of young gynaecologists. A recent survey by means of a questionnaire of leading centres for gynaecological oncology in Western Europe [10] showed that there is no uniform approach for postoperative radiotherapy in endometrial carcinoma. Postoperative radiotherapy was often the therapy of choice in high risk patients but wide variations were observed. High risk patients were considered as having poorly differentiated tumours and/or deep myometrial invasion.

Referral for radiotherapy seems to be more influenced by differences in opinion of the referring gynaecologists concerning the value of postoperative radiotherapy, than by the guidelines of a radiotherapy department. Differences in the referral pattern of the gynaecologists are not illogical because there is no conclusive evidence about the value of postoperative radiotherapy in stage I endometrial carcinoma. Indications for postoperative radiotherapy are not based on results of prospective randomised trials but rather on retrospective studies. One of the few prospective randomised studies is that of Aalders and colleagues [11], that investigated only the impact of two different radiotherapy approaches. After intravaginal radium irradiation, patients were randomised between external pelvic radiotherapy or no radiotherapy. In this study, no effect on survival of postoperative external radiotherapy could be established.

In our study, the only prognostic factors for survival were the depth of myometrial invasion, tumour differentiation and age. In the younger patient population, the depth of myometrial invasion was the most important prognostic factor, while in older patients tumour differentiation was the important prognostic factor. These results are difficult to explain when taking into account that, in the older age group, deeply invasive tumours were more frequently observed than in the younger age group. Moreover, the survival curves for patients older than 60 years with regard to tumour differentiation converge after a follow-up of 15 years. A possible explanation is that the risk of death due to other causes was much greater than the risk of death due to endometrial carcinoma; making these factors only statistically significant in subgroups. It is well known that endometrial carcinoma is associated with other health problems, such as obesity, late menopause, tamoxifen therapy, breast/colon cancer and diabetes [12]. Patients with endometrial carcinoma have higher risks of secondary cancers, with an average latency period from the first malignancy to the second of 4.5 years [13]. Of 1503 patients with endometrial carcinoma, 163 (10.8%) had multiple cancers, particularly breast cancer [14]. All these factors may explain why the studied patient population had an excess death rate over the normal Dutch female population. In previous studies [3, 4], an excess death rate over the normal Dutch female population was not established, but follow-up duration in both studies was maximally 13 and 17 years, respectively, and only patients receiving postoperative radiotherapy were included. The fact that recurrences of endometrial carcinoma after 4 years of follow-up are rare [3] indicates that the excess death rate was most probably not due to late recurrences of endometrial carcinoma, but due to existing co-morbidity, a view point which is corroborated by the fact that even after 10 years an increased death rate was found.

An advantage of postoperative radiotherapy on survival could not be established, even in the subgroups. A possible explanation is that the risk of a locoregional relapse after surgery alone is higher (±9%) [15] than after surgery followed by postoperative radiotherapy (4–5%) [3, 4]. However, after surgery alone, a successful approach with surgery and/or radiotherapy is still possible with success rates varying between 28 and 45% [3, 16], while rescue possibilities after surgery and radiotherapy are almost zero, resulting in similar failure figures of both approaches. The fact that both groups were comparable with respect to survival does not mean that there were no differences between both groups. Adjuvant progestogen may have played a certain role, although it was not in common use, and a positive effect is unlikely as a prospective randomised study concerning the usefulness of adjuvant progestogen for patients with stage I endometrial carcinoma showed no advantage [17]. Definitive conclusions cannot be drawn from this retrospective study and await the results of the PORTEC-study (PostOperative Radiotherapy for Endometrial Carcinoma). In this prospective trial

concerning stage I endometrial carcinoma, patients with superficial infiltrating, G1 tumours never received postoperative radiotherapy, while patients with deep infiltrating and G3 tumours always received postoperative radiotherapy. All other categories are randomised with stratification in respect to the depth of infiltration between radiotherapy or no radiotherapy. The Gynecologic Oncology Group (GOC) conducted the GOC Study no. 99, in which patients with stage IB and IIB endometrial carcinoma were randomised between postoperative pelvic radiation or no radiation [13], but the results are yet to be analysed.

In conclusion, the variation in referral is partly due to histological factors, but seems mostly to be due to differences in opinion between referring gynaecologists. The depth of myometrial invasion and grade of tumour differentiation were strongly associated with overall survival, but the impact of deep myometrial invasion was limited to patients younger than 60 years, while the impact of tumour differentiation was limited to patients older than 60 years. A clear benefit of postoperative radiotherapy could not be established.

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Acknowledgements—We wish to thank all gynaecologists united in the Gynaecological Working Party who participated in this study. We particularly acknowledge the staff of the Comprehensive Cancer Centre South, Eastern Section, Eindhoven, The Netherlands, for retrieving and reclassifying all patient data.