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Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008

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ABSTRACT

Background: Endometrial cancer (EC) occurs more frequently amongst women over 60 years old, who often also suffer from co-morbidity. Since treatment guidelines are derived from clinical trials that usually exclude such patients, nevertheless these guidelines are also applied for older EC patients. We assessed the independent influence of age and co-morbidity on treatment modalities and survival of patients with stage I EC in everyday clinical practice, thereby also examining the implementation of Dutch guidelines on treatment, since 2000.

Methods: All 2099 stage I EC patients diagnosed between 1995 and 2008 in the southern Netherlands were registered in the ECR (Eindhoven Cancer Registry) were included for analysis of the influence of age and co-morbidity on treatment and survival. For co-morbidity we used a modified version of Charlson's list, uniquely recorded in the ECR since 1993. A subgroup analysis was performed of patients who should have received adjuvant radiotherapy based on the risk factors advised in the Dutch guidelines of 2000. We considered five periods (1995–97; 1989–2000; 2001–03; 2004–06; 2007–08).

Results: Having two or more co-morbid conditions resulted in a significant reduction of receiving adjuvant radiotherapy (Odds Ratio: 0.6, 95% Confidence Interval (95% CI): 0.3–1.0)) but receiving adjuvant radiotherapy did not appear to improve survival. After adjustment for age, tumour stage, tumour grade, period of diagnosis and treatment, co-morbidity increased the risk of death, especially diabetes (Hazard Ratio (HR) for mortality: 2.9,95% CI: 2.2–4.0), a previous cancer (HR: 2.6, 95%CI: 1.9–3.7) and cardiovascular disease (HR: 2.3, 95%CI: 1.7–3.2). The combination of two or more co-morbid conditions resulted in a HR of 3.0 (95%CI: 2.2–3.9).

Conclusion: Co-morbidity decreased the likelihood of receiving adjuvant radiotherapy in patients with stage I EC qualifying to undergo this according to the Dutch guidelines of 2000. Whereas adjuvant radiotherapy did not seem to affect survival in those patients, co-morbidity significantly did.

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1. Background

Endometrial Cancer (EC) is the most common gynaecological cancer in industrialised countries. In the Netherlands it affects approximately 1700 women per year of whom 300 to 350 die each year.[1,2] Seventy to eighty percent of all cases of EC are diagnosed at an early stage (International Federation of Gynaecology and Obstetrics [FIGO] 1988 stage I) and generally have a good prognosis.[3] The tumour develops predominantly in women aged 60 years or older. In the Netherlands, as well as in the rest of the industrialised world, the incidence of EC has been increasing slightly.[2,4–8] This is due to increased life expectancy and changes in lifestyle factors, leading for example to obesity.[5,6] EC often develops in older women who, because of their age, are likely to have other chronic disabling conditions (co-morbidity).[7] Some of these conditions, such as diabetes, hypertension and obesity, are in themselves associated with an increased risk of EC.[4–8] For patients with serious co-morbidity, a physician might decide to alter standard oncological treatment due to an increased risk of side-effects or limited life expectancy.

Total abdominal hysterectomy with bilateral resection of the ovaries is the cornerstone of treatment for stage I EC. Up to the year 2000 adjuvant pelvic radiotherapy was advised for almost all stage I EC patients, except those with low-grade tumours and superficial invasion. Bases on the results of the Portec trial,[9] the guidelines were changed in 2000 into consideration of adjuvant radiotherapy only in the presence of two or thereof the risk factors (>50% myometrial invasion, grade 3 histological type, age $\geqslant$60 years). Adjuvant radiotherapy in this situation reduces the likelihood of loco regional recurrence by 3–10%, but has no impact on overall survival.[9–12]

This population-based study, carried out in a region with medium to large general hospitals only and two large radiation therapy centres, investigated the effect of co-morbidity uniquely recorded in the ECR, on the choice of treatment and survival rates in patients with stage 1 EC.

2. Methods

2.1. Data collection

All newly diagnosed patients (n = 2099) with stage I EC diagnosed between 1 January 1995 and 31 December 2008 were selected from the ECR (Eindhoven Cancer Registry), that registers data of all newly diagnosed patients with cancer occurring in 2.4 million inhabitants in the southern Netherlands. After notification from the pathological laboratories or the medical registration offices, trained registration clerks collected data from the medical records on diagnosis, tumour stage and treatment and since 1983 also serious co-morbidity with prognostic impact. The medical record is generally regarded as the most complete source of information on the patients past and current health status.[13] The list of co-morbidity is a modified version of the Charlson co-morbidity index (Table 1). Co-morbidity was defined as diseases that were present at the time of the cancer diagnosis.[14] In case of two different cardiovascular conditions each of them was registered. The completeness and accuracy of the co-morbidity data in the ECR were validated between 2001 and 2003[14] and only a slight under registration occurred (especially of cardiovascular conditions). Tumour stage was defined according to the FIGO staging system, based on postoperative information. FIGO stage I EC was divided into stage Ia (no myometrial invasion), Ib (less than 50% myometrial invasion) and Ic (more than 50% myometrial invasion). In the Netherlands, guidelines for primary treatment and adjuvant treatment as implemented in 2000, were based on the results of the randomised Portec I trial on adjuvant radiotherapy (1990–1997).[9]

Table 1 – Classification of co-morbidity, as recorded in the Eindhoven Cancer Registry.

Previous malignancies (except basal cell skin carcinoma and cervical carcinoma in situ)
Chronic obstructive pulmonary diseases
Cardiovascular diseases
Myocardial infarction
Heart failure
Angina pectoris
Cardiomyopathy
Valve prothesis (aorta or mitralis)
Intermittent claudication
Abdominal aneurysm
Thromboembolic events
Cerebrovascular diseases
Cerebrovascular accident
Hemiplegia
Hypertension
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other
Digestive tract diseases (Ulcerative disease, Chronic inflammatory diseases)
Urinary tract diseases
Connective tissue diseases
Dementia
Chronic infection

Furthermore, five hospitals in the ECR region participated in a separate study routine performance of pelvic lymph adenectomy for 237 patients with stage I EC from 1995 to 2004 (13% of the total population of this study). If the pelvic lymph nodes were negative, no radiotherapy was given, regardless of the presence of the aforementioned risk factors.[15] This resulted in a total of 71 (4%) patients who were not treated according to the Dutch guidelines of 2000.[16] We considered five periods (1995–97; 1998–2000; 2001–03; 2004–06; 2007–08), to analyse the influence on referral for adjuvant radiotherapy with these two studies in mind.

Vital status was available up to January 1 2009. In addition to results from passive follow-up data of the hospitals, information was also obtained from the Municipality Administration Database, in which deceased and emigrated persons in the Netherlands are registered via the civil municipal registries.

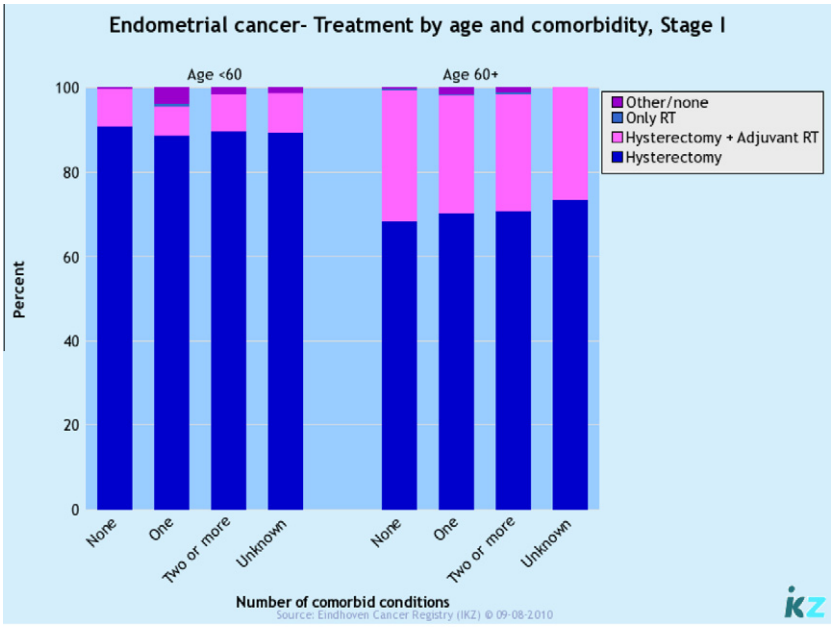
2.2. Statistical analysis

The prevalence of co-morbidity was analysed according to age (under 60 versus 60 and older).

For a subgroup analysis, a selection was made of patients who should have received adjuvant radiotherapy in accordance with the risk factors as advised in the current Dutch guidelines.[16] This selection was made for patients treated between 2000 and 2008 and led to 444 patients who should have received adjuvant radiotherapy. Prior to 2000, either gynaecologists participated in the Portec trial, or referred patients on their own insight, resulting in a heterogeneous approach, therefore patients diagnosed before 2000 were excluded from this subgroup analysis. After exclusion of patients ($n = 57$) with unknown grade, unknown co-morbidity and without a subdivision of stage I, 387 patients out of 444 remained for multivariate analysis. Logistic regression was used to investigate which factors influenced the likelihood of receiving adjuvant radiotherapy. First, the effect of the number of co-morbid conditions (0, 1, 2+) was evaluated. Thereafter, the effects of the most common types of co-morbidity (diabetes, cardiovascular disease, hypertension and previous malignancy) were also evaluated in separate models, each adjusted for the same covariates as the model for the number of co-morbid conditions (age, FIGO stage, grade and period of diagnosis). Crude 3-year and 5-year univariate survival rates were computed. Survival time was defined as the time from diagnosis to death. Patients who were still alive at the end of the study were censored on January 1 2009. The prognostic effects of age and number of co-morbid conditions on survival were estimated in a multivariate Cox regression model adjusted for stage, grade, period of diagnosis and radiotherapy. Comparable to logistic regression analyses, the prognostic effects on survival of the most common types of co-morbidity (diabetes, cardiovascular disease, hypertension and previous malignancy) were also evaluated in separate models, each adjusted for the same covariates as the model for the number of co-morbid conditions.

3. Results

The 2099 patients newly diagnosed with stage I EC during 1995 and 2008 had a mean age of 64 (range 28–91) and 66% were 60 years or older at the time of diagnosis. In Fig. 1, the treatment modalities are shown according to age and co-morbidity. In patients aged 60 years and older, the percentage receiving adjuvant radiotherapy were more than threefold higher (26–31%) as compared to those younger than 60 years of age (7–9%). In 98% of patients, hysterectomy was performed. Co-morbidity was present in 59% of patients receiving a hysterectomy. So co-morbidity did not affect the choice for hysterectomy. Less than 1% received only radiotherapy. Respectively ten patients (1.2%) in the group younger than 60 years of age and twelve (1.0%) patients of 60 years and older did not receive either hysterectomy or radiotherapy. Some of them received a not specified type of surgery. Information about the implementation of the Dutch guidelines (published in 2000)[13] is shown in Table 2. The two out of three risk factors rule for receiving adjuvant radiotherapy (age $\geqslant$60 years, more than 50% invasion of the myometrium, and grade 3 disease) was retrospectively used for the total population of 2099 patients (Table 2). The percentage of patients receiving adjuvant radiotherapy, although this was not recommended according to the guide-



Hysterectomy = hysterectomy and bilateral oophorectomy
RT= radiotherapy

Fig. 1 – Treatment of stage I endometrial cancer according to age and number of co-morbid conditions in a population of $n = 2099$ unselected patients in the Eindhoven Cancer Registry (ECR) region. Period of diagnosis 1995–2008.

Table 2 – Treatment recommendations according to the Dutch guidelines (2000) and actual treatment delivery during 1995–1997; 1998–2000; 2001–2003; 2004–2006; 2007–2008.

Treatment according to guidelines	Treatment given				
	N (%) Hysterectomy	N (%) Hysterectomy and Adj RT[a]	n RT[b]	N (%) No Hysterectomy and no Adj RT[c]	Total
1995–1997					
Hysterectomy	**199 (79%)**	46 (18%)	2 (1%)	4 (2%)	251
Hysterectomy and Adj RT[a]	54 (45%)	64 (54%)	1 (1%)	0	119
1998–2000					
Hysterectomy	275 (94%)	15 (5%)	0	2 (1%)	292
Hysterectomy and Adj RT[a]	62 (47%)	69 (53%)	0	0	131
2001–2003					
Hysterectomy	293 (95%)	11 (4%)	2	3 (1%)	309
Hysterectomy and Adj RT[a]	59 (46%)	67 (53%)	0	1 (1%)	127
2004–2006					
Hysterectomy	331 (93%)	12 (2%)	0	11 (5%)	354
Hysterectomy and Adj RT[a]	64 (39%)	100 (60%)	0	2 (1%)	166
2007–2008					
Hysterectomy	229 (95%)	12 (5%)	0	0	241
Hysterectomy and Adj RT[a]	48 (44%)	59 (54%)	2 (1%)	0	109
1995–2008					
Hysterectomy	1327 (92%)	98 (7%)	4	20 (1%)	1447
Hysterectomy and Adj RT[a]	287 (44%)	359 (55%)	1	5 (1%)	652
	1614 (77%)	457 (22%)	5	23 (1%)	2099
2000–2008[c]					
Hysterectomy	942 (94%)	49 (5%)	2	10 (1%)	1003
Hysterectomy and Adj RT[a]	195 (44%)	244 (55%)	2	3 (1%)	444

[a] Adj RT = adjuvant radiotherapy.
[b] RT = radiotherapy.
[c] For deduction of numbers for subgroup analysis in Table 3.

lines, was 18% (underlined numbers in Table 2) in the first period from 1995 to 1997 and decreased to 2–5% in the following periods. The group who underwent a hysterectomy without adjuvant radiotherapy as recommended increased from 79% in the first period from 1995 to 1997, to 93–95% in the following periods (bold numbers in Table 2). The percentage of patients who should have received adjuvant radiotherapy according to the guidelines but who were not referred varied between 39% and 47%.

Table 3 shows the results of a multivariate analysis of determinants of referral in the 387 patients who should have received adjuvant radiotherapy according to the guidelines.[13] Patients with Stage Ic had a significant influence on whether patients received radiotherapy (Odds Ratio (OR) was 4.7 (95% CI 1.4–16)). Patients with two or more co-morbid conditions received significantly less adjuvant radiotherapy with an OR of 0.6 (95% CI: 0.3–0.96).

For univariate and multivariate survival analyses, patients were excluded because of missing information on co-morbidity ($n = 207$), grade ($n = 92$) and stage ($n = 30$) leaving 1770 patients for further analysis.

In Table 4, crude 3 and 5-year univariate survival and HR (Hazard Ratio) for mortality are shown according to age, stage, grade, number of concomitant conditions, type of co-morbidity and also taking primary treatment into account.

Five-year survival for patients aged 60 years and older was 82%, a drop of 11% compared to 93% 5-year survival for those younger than 60 years of age. For patients with two or more co-morbid conditions the five-year survival was 73% versus 91% for those without co-morbidity. For patients with diabetes five year survival was 74% for patients with cardiovascular disease this was 76% and for patients with a previous malignancy this was 75%. Period of diagnosis had no independent influence on survival. The multivariate HR for mortality was 3.0 (95%CI: 2.1–4.2) for patients aged 60 years and older compared to younger patients. The HR for mortality for patients with diabetes versus no co-morbidity was 2.9 (95% CI: 2.2–4.0), 2.6 (95% CI 1.9–3.7) for previous malignancy versus no co-morbidity and 2.3 (95% CI: 1.7–3.2) for cardiovascular disease versus no co-morbidity. The multivariable HR for mortality for adjuvant radiotherapy was 1.0 (95% CI:0.7–1.3).

4. Discussion

Co-morbidity had no influence on the resection rate in this population of 2099 patients diagnosed with stage I EC between 1995 and 2008; 98–99% of the patients underwent hysterectomy. This was also seen in other tumours were there are no alternatives for surgery, for example in patients with colorectal cancer.[17,18] In contrast, we found that patients with

Table 3 – Multivariate regression analysis of odds of receiving adjuvant radiotherapy (OR) in a subgroup of 387[b] patients diagnosed during 2000–2008 based on two out of three rule of the Dutch treatment guidelines.

		n	%	OR	95% CI[a]
Age	<60 years	13	3.4	1.0	–
	⩾60 years	374	97	1.6	0.5–5.6
FIGO	IA	18	4.6		
	IB	36	9.3	1.8	0.5–6.7
	IC	333	86	4.7	1.4–16
Period of diagnosis	2000–2002	100	26	1.0	–
	2003–2005	131	34	1.0	0.6–1.7
	2006–2008	156	40	1.5	0.9–2.6
No. of co-morbidities	0	112	29	1.0	–
	1	148	38	0.8	0.5–1.3
	2+	127	33	0.6	0.3–0.96
Co-morbidity	Cardiovascular	95	25	0.8	0.4–1.3
	Diabetes	85	27	0.8	0.5–1.3
	Hypertension	166	43	0.9	0.6–1.3
	Previous cancer	56	14	0.7	0.4–1.2

[a] 95% Confidence Interval.
[b] 2000–2008 *n* = 444 (Table 2) minus 57 patients with incomplete data: 387 patients were left for multivariate regression analysis.

Table 4 – Crude univariate three and five-year survival and multivariable Hazard ratios (HR) for patients with endometrial cancer in the south of the Netherlands 1995–2008 (*n* = 1770).

		n	%	3-year survival (%)	5-year survival (%)	HR [c]	[d]95%CI
Age	<60 years	579	33	96	9	Ref.	
	⩾60 years	1191	67	88	82	3.0	2.1–4.2
FIGO[a]	IA	274	15	91	87	Ref.	
	IB	902	51	93	89	1.0	0.7–1.4
	IC	594	34	87	80	1.4	1.0–2.1
Grade	Low/intermediate	1531	87	93	89	Ref.	
	High	239	14	79	67	2.5	1.9–3.2
Period of diagnosis	1995–1997	332	19	91	85	Ref.	
	1998–2000	370	21	90	85	0.8	0.6–1.0
	2001–2003	341	19	90	87	0.8	0.5–1.1
	2004–2006	418	24	93	–	0.7	0.5–1.1
	2007–2008	309	17	–	–	0.8	0.4–1.7
Number of co-morbidity	0	721	41	95	91	Ref.	
	1	605	34	92	88	1.4	1.0–1.9
	2+	444	25	82	74	3.0	2.2–3.9[f]
Type co-morbidity[b]	Cardiovascular	281	16	83	76	2.3	1.7–3.2
	Diabetes	304	17	85	74	2.9	2.2–4.0
	Hypertension	596	34	88	82	1.8	1.4–2.4
	Previous cancer	232	13	83	75	2.6	1.9–3.7
Primary treatment	Hysterectomy	1366	77	92	88	Ref.	
	Hysterectomy + ART[e]	404	23	87	79	1.0	0.7–1.3

[a] FIGO = International Federation of Gynaecology and Obstetrics staging system 1988.
[b] Reference category: no co-morbidity.
[c] HR = multivariate hazard ratio for death.
[d] CI = Confidence Interval.
[e] ART = adjuvant radiotherapy.
[f] Statistically significant.

two or more co-morbid conditions were less likely to receive adjuvant radiotherapy, even after implementation of the Dutch guidelines in 2000.[13] Survival was clearly poorer for patients with co-morbidity compared to patients without co-morbidity, especially for those with diabetes, cardiovascular disease and previous malignancy.

In 1999, just before the implementation of the new Dutch guidelines, a decrease in the proportion of patients

receiving adjuvant radiotherapy already occurred (Table 2). This can be explained by the fact that in 1999, most of the gynaecological oncologists and radiotherapists had already been informed about the results of the Portec I trial,[9] which only recommended referral for adjuvant radiotherapy when patients had two out of the three risk factors (age $\geqslant$60 years, more than 50% invasion of the myometrium, and grade 3 disease). On the other hand, the percentage of patients indicated to receive radiotherapy due to the risk factors listed above and in whom adjuvant radiotherapy was not performed, remained considerable (between 39% and 47%). This percentage was neither influenced by the implementation of the guidelines nor by a study performed in five of the hospitals in the ECR region.[12] This study on lymph-adenectomy in stage I EC was conducted from 1998 to 2004. In this study only 71 patients (or 4%) did not receive adjuvant radiotherapy when lymph nodes were negative, although two of the risk factors listed above were positive.

In the multivariate analysis on a subgroup of 387 patients who had two out of the above mentioned risk factors and should have received adjuvant radiotherapy according to the Dutch guidelines of 2000,[13] a significant reduction in receiving adjuvant radiotherapy was found, when two or more co-morbid conditions were present. Several studies have shown that patients with co-morbidity are less likely to be treated according to guidelines than patients without co-morbidity.[2,4–8] A publication on treatment guidelines for breast cancer has shown that co-morbidity was the most frequently stated reason for deviating from treatment guidelines (11 out of 18 motivated deviations).[19,20] Serious co-morbidity can be legitimate reason for deviating from treatment guidelines if the life expectancy of a patient is significantly reduced by it. Besides that, 31% of treatment omissions were due to patient preference. The Portec 1 trial[9] has shown that protocol violations occurred in the radiotherapy group. In twelve out of 23 patients radiotherapy was refused by patients. Reasons for not recommending adjuvant radiotherapy for gynaecologists were: old age, co-morbidity or negative judgment of its benefit. The value of postoperative radiotherapy is controversial, although pelvic radiotherapy reduces vaginal and pelvic relapse, distant metastases still occur in this group and no survival benefit has been confirmed.[9–12] When a patient either or not with serious co-morbidity, is frail or older than 80 years of age, thorough follow up is a reasonable alternative, because high salvage rates with radiotherapy are reported amongst patients with local recurrence.[9–12]

As was expected, age and co-morbidity turned out to be highly predictive factors for survival after adjustment for tumour stage, tumour grade, period of diagnosis and treatment. However the decrease in survival of 15–17% in patients with cardiovascular disease, previous malignancy and diabetes as compared to patients without co-morbidity are impressive. Clinical and biological interaction between diabetes and endometrial cancer is explained partly by the presence of higher levels of insulin in Type 2 diabetes mellitus, which results in higher levels of bio-available oestrogens, partly due to the enhancing effect of insulin–like growth factors resulting in endometrial mitogenesis.[4–8,21,22]

Cardiovascular disease, hypertension and diabetes are related to obesity. In obese patients the peripheral conversion of androstenedione to estrone by adipocytes leads to a chronic low-level increase in oestrogen exposure leading to an increased risk of EC.[5] Because no information on the disease-specific cause of death was available in our study, we cannot answer the question of whether co-morbidity results in earlier death or whether it affects the course of EC, for example, by earlier recurrence or metastasis. The different pathways to a diabetes-related mortality risk are not yet known. Patients have a poorer prognosis in case of a previous cancer as co-morbid condition. This is possibly due to therapeutic influence like tamoxifen use in case of previous breast cancer or radiation therapy in case of previous cervical cancer or colorectal cancer.[23,24,26,27] Tamoxifen and previous radiation therapy has been associated with a higher proportion of unfavourable uterine tumour subtypes with worse survival.[23,24,26] Furthermore a lower social economic status (SES) is related to an increased prevalence of co-morbidity, with more frequent diabetes, obesity and increased risk of breast and endometrial cancer and a poorer overall prognosis.[25] Obesity may affect the selection of treatment modalities for patients with endometrial cancer, although several studies suggest that comprehensive surgical staging for endometrial carcinoma can be performed in obese patients with similar operative morbidity as in patients of ideal body weight. In this population based study we found that surgery was equally performed in patients with co-morbidity and in patients without co-morbidity.[26,27] Poorer survival in patients with previous cancer can also be related to prognosis of the first malignancy.

Although this population-based study had the advantage of being able to avoid a selection bias, detailed information on performance status of the patient and treatment-related effects other than mortality such as recurrence and long term complications were not available. These and other factors, such as cognitive disorders and frailty, also play a role in how patients are selected for effective and safe treatment.[17] Information about staging procedures was also not available. Moreover, the cause of death was unknown. We could therefore not evaluate whether patients with co-morbidity had a higher risk of dying as a result of endometrial cancer. To understand referral patterns we need alternative strategies, because of the large individual variations in physical and mental conditions and personal preferences of patients and physicians prevailing influence on decision-making process.

In conclusion, co-morbidity did not affect the proportion of patients with stage I endometrial cancer undergoing hysterectomy but had a strong association with not receiving adjuvant radiotherapy. The receipt of adjuvant radiotherapy did not appear to affect survival, which was clearly poorer in patients with co-morbidity, especially those with diabetes, previous malignancy and cardiovascular disease. The limited advantages of better loco-regional control of adjuvant radiotherapy should be weighted against the real dangers of co-morbidity and these patients might need a more explicit multidisciplinary surveillance in order to improve survival rates and quality of life by avoiding complications and promoting specific rehabilitation by preventing overweight, obesity and type II diabetes.

Conflict of interest statement

None declared.

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