Survival Benefit with Radiation Therapy in Node-Positive Breast Carcinoma Patients

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Background and Purpose: Postoperative radiation therapy (RT) has been the subject of discussion, especially in patients with one to three positive lymph nodes (≤ 3 pN+) in the axillary dissection. The authors investigated whether postoperative RT provides a survival benefit for pT1–2 pN+ breast cancer patients.
Patients and Methods: Patients included were selected from the SEER database (NCI – Surveillance, Epidemiology and End Results, release 2000; n = 24,410) and the UZ Brussel database (1984–2002; n = 1,011) according to the following criteria: women aged 25–95, no previous cancer, unilateral pT1–pT2 breast tumors, total mastectomy (ME) or breast-conserving surgery (BCS), postoperative RT, and an axillary dissection showing at least one pathologic lymph node.
Results: The overall survival (OS) of patients in the SEER and UZ Brussel databases who received postoperative RT was identical. However, patients in the SEER database who did not receive RT had a significantly worse outcome ($p < 0.0001$). After ME or BCS, all patients (SEER and UZ Brussel) who had ≥ 4 pN+ and received RT had comparable outcomes after 15 years. The 15-year OS in the subgroup with ME and ≤ 3 pN+ nodes was 57.0% and 46.6% ($p = 0.0004$) with RT (UZ Brussel) and without RT (SEER), respectively. For BCS and ≤ 3 pN+, the same significant difference in OS at 15 years was seen: 63.8% after RT (UZ Brussel) and 60.4% without RT (SEER; $p = 0.0029$).
Conclusion: RT provides a survival benefit in patients with ≤ 3 or ≥ 4 pN+; the indication for postoperative RT should therefore be adapted in future consensus meetings.

Key Words: Breast carcinoma · Postoperative radiotherapy · One to three positive axillary nodes

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Überlebensvorteil bei postoperativer Strahlentherapie bei Patientinnen mit Mammakarzinom und Lymphknotenbefall

Hintergrund und Ziel: Der Nutzen einer postoperativen Strahlentherapie (RT) wird diskutiert, insbesondere bei Patientinnen mit einem bis drei befallenen Lymphknoten (≤ 3 pN+). In der vorliegenden Studie wird untersucht, ob die postoperative RT für Patientinnen mit Mammakarzinom im Stadium pT1–2 pN+ einen Überlebensvorteil bietet.
Patienten und Methodik: Die Patientinnen wurden aus der SEER-Datenbank (NCI – Surveillance, Epidemiology and End Results, Ausgabe 2000; n = 24 410) und der Datenbank des UZ Brussel (1984–2002; n = 1 011) ausgewählt. Berücksichtigt wurden folgende Kriterien: Frauen im Alter von 25–95 Jahren, keine Krebserkrankung in der Vorgeschichte, unilaterale Mammakarzinome Stadium pT1–pT2, Mastektomie (ME) oder brusterhaltende Operation (BCS [„breast-conserving surgery"]), postoperative RT und Axilladissektion mit mindestens einem befallenen Lymphknoten.
Ergebnisse: Das Gesamtüberleben (OS [„overall survival"]) der Patientinnen aus der SEER-Datenbank und der Datenbank des UZ Brussel, die postoperativ bestrahlt worden waren, war identisch. Demgegenüber fand sich bei Patientinnen aus der SEER-Datenbank, die keine postoperative RT erhalten hatten, ein schlechteres Ergebnis ($p < 0{,}0001$). Unabhängig von der Art des operativen Eingriffs (ME oder BCS) zeigten alle Patientinnen (SEER und UZ Brussel), die ≥ 4 pN+ aufwiesen und eine RT erhalten hatten, vergleichbare Resultate nach 15 Jahren. Das 15-Jahres-OS in der Untergruppe mit ME und ≤ 3 pN+ betrug 57,0% und 46,6% ($p = 0{,}0004$) mit RT (UZ Brussel) bzw. ohne RT (SEER). Bei Patientinnen nach BCS und ≤ 3 pN+ zeigte sich der gleiche signifikante Unterschied im OS nach 15 Jahren: 63,8% nach RT (UZ Brussel) und 60,4% ohne RT (SEER; $p = 0{,}0029$).
Schlussfolgerung: Die RT bietet sowohl für Patientinnen mit ≤ 3 als auch mit ≥ 4 pN+ einen Überlebensvorteil; deshalb sollte in künftigen Konsensuskonferenzen die Indikationsstellung für eine postoperative RT angepasst werden.

Schlüsselwörter: Mammakarzinom · Postoperative Strahlentherapie · Ein bis drei befallene Lymphknoten

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Introduction

In Western countries, breast cancer is the most common cancer in women and the incidence is increasing. In Belgium, 6,628 new cases were reported in 1998 which accounted for 35.5% of cancers in females. In 1997, 2,416 deaths from breast cancer were reported [16]. Radiation therapy (RT) of the axillary and supraclavicular lymph node area in women with breast cancer and one to three positive lymph nodes (≤ 3 pN+) is still widely debated [8, 14, 26, 27]. In consensus reports and guidelines, no postoperative RT to the lymph node area is recommended when ≤ 3 pN+ are involved, since it is assumed that only patients at high risk of locoregional recurrence benefit from postoperative RT [9, 24]. After the publication of two major randomized prospective trials showing improved survival after RT in all node-positive pre- and perimenopausal women, Kuske stated, in 1999, that the greatest benefit might be seen in women with ≤ 3 pN+ [13, 19, 22]. According to a recent publication by Overgaard et al. survival benefit was at least equally beneficial in patients with ≤ 3 pN+ [20]. In a previous publication, we stated that postoperative RT in node-negative breast cancer patients was also beneficial [41]. Since the inauguration of our RT department, all patients with invasive breast carcinoma systematically receive postoperative RT, irrespective of the number of lymph nodes involved. Since we do not have a reference population without postoperative RT, patients in the SEER database 1988–1997 (NCI – Surveillance, Epidemiology, and End Results, release 2000) [32] are used to compare and evaluate RT treatment.

Table 1. Characteristics of the patients with pT1–2 pN+ breast cancer from the SEER and UZ Brussel databases. ER: estrogen receptor; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; N_{tot}: total number of nodes dissected; PR: progesterone receptor; SEER: Surveillance, Epidemiology and End Results.

Tabelle 1. Eigenschaften der Patientinnen mit Mammakarzinom im Stadium pT1–2 pN+ aus der SEER- und der UZ-Brussel-Datenbank. ER: Östrogenrezeptor; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; N_{tot}: Gesamtzahl entfernter Lymphknoten; PR: Progesteronrezeptor; SEER: Surveillance, Epidemiology and End Results.

	UZ Brussel (n = 1,011) n (%)	SEER data (n = 24,410) n (%)
Age* (years), mean (range)	57.4 (26–88)	57.8 (25–95)
< 50 years	323 (31.9)	8,502 (34.8)
50–60 years	261 (25.8)	5,372 (22.0)
> 60 years	427 (42.2)	10,536 (43.2)
Stage*		
IIA (T1 N1)	366 (36.2)	11,647 (47.7)
IIB (T2 N1)	616 (60.9)	11,267 (46.2)
IIIA (T1–2 N2)	29 (2.9)	1,496 (6.1)
Histopathologic grading*		
Well/moderately	470 (46.5)	8,485 (34.8)
Poorly/undifferentiated	323 (31.9)	9,415 (38.6)
Unknown	218 (21,6)	6,510 (26,6)
Receptor status*		
ER+	531 (52.5)	12,790 (52.4)
ER–	251 (24.8)	4,359 (17.9)
ER unknown	229 (22.7)	7,261 (29.7)
PR+	467 (46.2)	11,209 (45.9)
PR–	292 (28.9)	5,626 (23.0)
PR unknown	252 (24.9)	7,575 (33.1)
N_{tot} dissected (mean)	17.2	16.0
Positive nodes*		
≤ 3	640 (63.3)	16,136 (66.1)
≥ 4	371 (36.7)	8,274 (33.9)
N+ ratio*		
≤ 20%	571 (56.5)	14,313 (58.6)
21–65%	314 (31.1)	7,267 (29.8)
> 65%	126 (12.5)	2,830 (11.6)
Tumor site*		
Left breast	530 (52.4)	12,522 (51.3)
Right breast	481 (47.6)	11,888 (48.7)
Quadrant*		
Inner	181 (17.9)	2,687 (11.0)
Other	830 (82.1)	21,723 (89.0)

*$p < 0.001$

Patients and Methods

Patients included in this analysis were selected from the SEER database and the UZ Brussel database according to the following criteria: women aged 25–95, no previous diagnosis of cancer, unilateral pT1–pT2 primary breast tumors, mastectomy (ME) or breast-conserving surgery (BCS), and in whom axillary dissection was performed with at least one positive node.

Patient Characteristics in the UZ Brussel Database

From 1984 to July 2002, 3,517 breast cancer patients treated at our department were available for retrospective analyses. As shown in Table 1, 1,011 patients met all inclusion criteria for further evaluation. An ME was performed in 725 cases (71.7%), and 286 patients (28.3%) underwent BCS. All patients had an axillary lymph node dissection followed by postoperative RT.

Patient Characteristics in the SEER Database

From 1988 to 1997, 24,410 patients in the SEER database with the same characteristics were evaluated. An ME was performed in 17,116 patients (70.1%), and 7,294 patients (29.9%) underwent BCS. Patient characteristics are reported in Table 1.

Statistical Analysis

For statistical calculations, computer software JMP® (SAS Institute Inc., Cary, NC, USA) was used. The univariate analysis of survival was performed with the Kaplan-Meier method [11]. An event was defined as death from any cause for overall survival (OS). Breast cancer survival time was defined as the length of time from the date of diagnosis to the date of an event or the date last known to be alive. Reported p-values are two-sided and a p-value < 0.05 was considered statistically significant. The multivariate analyses were performed using Cox proportional hazard models without interactions [5]. The proportional hazard model fit was assessed using the likelihood ratio. Variables included were: age, right or left breast, grading, tumor stage, type of surgery, quadrant, histology, nodal ratio (= number of positive nodes divided by number of nodes examined, expressed in percentages), estrogen (ER) and progesterone receptor (PR) status, database origin. All factors were treated as simple categorical variables. To avoid the effect of linear assumption and the requirement for complex transforms [33, 36], continuous variables were categorized as follows: according to age, patient groups of < 50 years, between 50 and 60 years, and > 60 years were defined; according to the nodal ratio, patient groups with a ratio ≤ 20%, between 21% and 65%, and > 65% were defined [39]; for tumor size, only T-stage was used, with T1 ≤ 2 cm, and T2 > 2 cm and ≤ 5 cm. We did not use Propensity Score analysis on consideration that it does not adjust for unobserved covariates [25], the advantage over other methods is unclear [31], overfitting might miss significant covariates [28], whereas our prior analyses using conventional methods correctly anticipated the results of randomized clinical trials [37, 40]. Factors examined in the univariate analyses were also examined in the multivariate analyses. Reported p-values are two-sided and a p-value < 0.05 was considered statistically significant.

Radiotherapy Characteristics in the UZ Brussel Database

Patients were treated with standard medial and lateral wedged tangential breast portals and an anterior field on the axillary and supraclavicular lymph node region after preceding simulation. Computed tomography scan-based planning was performed. Until 1994, two-dimensional planning was performed; afterwards, a three-dimensional planning system was used. Megavoltage (MV) photon beams were used to deliver RT. The dose on the breast or chest wall was prescribed at the isocenter; the dose on the lymph nodes was calculated at 3 cm depth. Patients were irradiated five times weekly with 2 Gy per fraction receiving a dose of 46–50 Gy to the supraclavicular and axillary region, the chest wall (ME) or the breast (BCS). In cases of BCS, an additional booster dose of 20–16 Gy was given at the primary tumor bed.

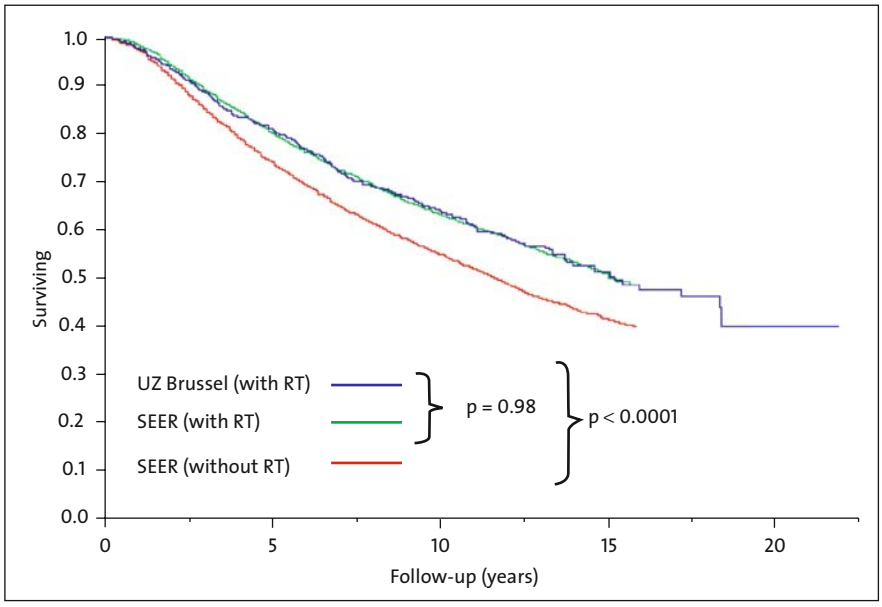

Figure 1. Overall survival of patients from the Surveillance, Epidemiology and End Results (SEER) database with and without radiation therapy compared with those from the UZ Brussel database.

Abbildung 1. Gesamtüberleben der Patientinnen aus der SEER-Datenbank (Surveillance, Epidemiology and End Results) mit und ohne Strahlentherapie im Vergleich mit den Patientinnen aus der Datenbank des UZ Brussel.

Radiotherapy Characteristics in the SEER Database

In the SEER database, detailed data concerning the RT technique, treatment fields, dose or timing was not available. When ≤ 3 pN+ were involved, 66.8% of the patients (n = 10,785) did not receive postoperative RT, while 33.2% (n = 5,351) were irradiated. In case of ≥ 4 pN+, only 39.8% of the patients (n = 3,289) received postoperative RT, while the other 60.2% (n = 4,985) did not.

Results

The OS of patients in both SEER and UZ Brussel databases receiving postoperative RT was identical. However, patients in the SEER database who did not receive RT had a significantly worse outcome (Figure 1). Locoregional recurrence was seen in 4.15% of patients

Table 2. Overall survival after mastectomy in different lymph node subgroups with or without radiation therapy (RT). SEER: Surveillance, Epidemiology and End Results.

Tabelle 2. Gesamtüberleben nach Mastektomie in den verschiedenen Lymphknotenuntergruppen mit oder ohne Strahlentherapie (RT). SEER: Surveillance, Epidemiology and End Results.

	≥ 4 positive nodes			≤ 3 positive nodes	
	UZ Brussel (+ RT) (n = 284)	SEER (+ RT) (n = 1,853)	SEER (no RT) (n = 4,547)	UZ Brussel (+ RT) (n = 441)	SEER (no RT) (n = 9,803)
5 years (%)	70.2	67.5	63.1	85.4	78.9
10 years (%)	45.4	47.2	41.0	70.9	60.9
15 years (%)	30.0	32.6	29.2	57.0	46.6
		p = 0.591			p = 0.0004
			p = 0.0001		

Table 3. Overall survival after breast-conserving surgery in different lymph node subgroups with or without radiation therapy (RT). SEER: Surveillance, Epidemiology and End Results.

Tabelle 3. Gesamtüberleben nach brusterhaltender Operation in den verschiedenen Lymphknotenuntergruppen mit oder ohne Strahlentherapie (RT). SEER: Surveillance, Epidemiology and End Results.

	≥ 4 positive nodes			≤ 3 positive nodes		
	UZ Brussel (+ RT) (n = 87)	SEER (+ RT) (n = 1,436)	SEER (no RT) (n = 438)	UZ Brussel (+ RT) (n = 199)	SEER (no RT) (n = 961)	SEER (+ RT) (n = 4,439)
5 years (%)	76.7	75.2	67.4	88.5	79.3	87.4
10 years (%)	58.7	56.0	52.5	82.4	66.2	73.1
15 years (%)	58.3	44.6	39.2	63.8	60.4	61.1
		p = 0.3083			p = 0.0029	
			p = 0.0166			p = 0.0001

(n = 42) treated in the UZ Brussel: 45.2% (n = 19) in patients with ≤ 3 pN+, 54.8% if ≥ 4 pN+. In SEER, no data about this issue are available.

After Mastectomy

Patients in both SEER and UZ Brussel databases who had ≥ 4 pN+ and who received RT after ME had comparable outcomes (Table 2). However, a subpopulation in SEER did not receive postoperative RT. The outcome of these patients (SEER, ≥ 4 pN+ and no RT) was significantly worse than in the group receiving RT (p = 0.0001). In the categories of patients with ≤ 3 pN+, the 5-, 10-, and 15-year OS rates improved with RT (Table 2). For the UZ Brussel ME patients (with RT) with ≤ 3 pN+, the OS was 85.4%, 70.9%, and 57% at 5, 10, and 15 years, respectively. In the SEER database (without RT), the OS was 78.9%, 60.9%, and 46.6% at 5, 10, and 15 years (p = 0.0004).

After Breast-Conserving Surgery

Patients in both SEER and UZ Brussel databases who had ≥ 4 pN+ and who received RT had comparable results (Table 3). Again, the subgroup in SEER that did not receive postoperative RT did significantly worse (p = 0.0166). In patients with ≤ 3 pN+, OS rates improved with RT (SEER and UZ Brussel patients; Table 3). Patients in SEER who were not subjected to postoperative RT had a significantly poorer prognosis (p = 0.0001 SEER with RT vs. SEER without RT; and p = 0.0029 SEER without RT vs. UZ Brussel with RT).

Multivariate Analyses of Variables

Multivariate analyses showed that all variables (except left/right breast) were important prognostic factors. N+ ratio was clearly significant (p < 0.0001). Patient treated in the UZ Brussel or the SEER group with RT had a similar outcome; patients in SEER without RT did significantly worse (p < 0.0001) (Table 4).

Multivariate Analyses of Variables for Survival after Stratification for Surgery

In both groups, ME and BCS, the analyses were significant for N+ ratio (p < 0.0001). Comparable results were seen for patients in the "SEER no RT" group which had a significantly poorer outcome (p = 0.0001) than patients receiving postoperative RT (SEER or UZ Brussel: Table 5).

Table 4. Multivariate analyses of variables for survival (n = 25,421). ER: estrogen receptor; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; PR: progesterone receptor; RT: radiotherapy; SEER: Surveillance, Epidemiology and End Results.

Tabelle 4. Multivarianzanalysen der Variablen für die Überlebensraten (n = 25 421). ER: Östrogenrezeptor; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; PR: Progesteronrezeptor; RT: Strahlentherapie; SEER: Surveillance, Epidemiology and End Results.

Variables		Hazard ratio*	Confidence intervals	p-value
Age	< 50 years	1		
	50–60 years	1.13	1.07–1.19	< 0.0001
	> 60 years	2.02	1.92–2.11	
Breast	Right	0.99	0.98–1.01	0.68
	Left	1		
Grading	1–2	0.85	0.82–0.87	< 0.0001
	3–4	1		
T-stage	T1	0.82	0.80–0.83	< 0.0001
	T2	1		
Surgery	BCS	0.88	0.83–0.93	< 0.0001
	ME	1		
Quadrant	Inner	1.15	1.08–1.22	< 0.0001
	Other	1		
Histology	Duct cell	1.07	1.02–1.12	0.004
	Other	1		
N+ ratio	≤ 20%	1		< 0.0001
	21–65%	1.51	1.45–1.58	
	> 65%	2.53	2.40–2.67	
ER receptor status	Negative	1.22	1.14–1.30	< 0.0001
	Positive	1		
PR receptor status	Negative	1.16	1.09–1.22	< 0.0001
	Positive	1		
Database	SEER no RT	1.19	1.14–1.25	< 0.0001
	SEER with RT	0.98	0.94–1.03	
	UZ Brussel	1		

*Hazard ratio < 1 indicates a favorable prognosis to reference (= 1)

Discussion

This nonrandomized retrospective analysis compares patients included in two different databases (UZ Brussel single-institution and multiinstitutional SEER database). OS of patients is exactly the same when treated with surgery and postoperative RT (Figure 1). In both databases, all the different variables are present in both groups of patients with ≥ 4 pN+. Patients uniformly treated with ME, axillary clearance and RT have comparable OS at 15 years (p = 0.59). Also, after BCS, axillary clearance and RT, there is no significant difference in OS at 15 years (p = 0.31). This suggests that there is no difference between patients in the two databases; the different variables are equally present in the SEER and UZ Brussel databases. If we accept this for the patient with ≥ 4 pN+, then there is no reason why it should not be true for patients with ≤ 3 pN+.

For the UZ Brussel patients with ≤ 3 pN+ (+ RT), 15-year OS results do differ significantly from those in the SEER database without RT (p < 0.0004 after ME; and p = 0.0029 after BCS). This indicates that – comparing the two databases – adding RT in women with ≤ 3 pN+ improves survival. This patient subgroup has a smaller burden of micrometastatic disease which can be eradicated by adding locoregional RT as stated by Van de Steene et al. and Stranzl et al. [29, 35].

Multiple randomized RT trials have included both node-negative and node-positive patients, but no stratification according to the degree of nodal involvement was performed. Overview analyses demonstrated that RT reduces local recurrences irrespective of nodal status. A reduction in breast and overall mortality could only be found in node-positive patients. This led to the consensus treating high-risk patients (i.e., primary tumor > 5 cm or ≥ 4 pN+) [4, 9, 23, 24]. An exception could be made in women with medial tumors, ≥ 4 pN+ and an ME. In this subgroup of patients the favorable effect of RT may also be the offset of late cardiac morbidity.

During the past decade, major effort was made to optimize RT (dose, fractionation, and treatment technique), so no RT-related excess of non-breast cancer death or major toxicity was found after several years of follow-up [7, 10, 30, 38].

In node-positive patients, adding locoregional RT may be essential in preventing secondary dissemination from residual locoregional disease, and could increase the potential for cure. Three recently published randomized trials (the British Columbia study, the EBCTCG 2005, and a subgroup analysis of the DBCG 82b&c trials investigating subgroups of breast cancer patients with ≤ 3 pN+ and postoperative RT) demonstrated that RT could improve OS [4, 17–19, 23]. This survival advantage was also found in "the combined dataset" analysis of the EORTC [34]. Four formerly published trials demonstrated that local recurrence rate was much higher for patients with ≤ 3 pN+ who had no adjuvant RT: 30% in the Danish chemotherapy trial [18]; 33% in the British Columbia trial [23]; 31% in the Danish tamoxifen trial [19], and 16% in the study of Cheng et al. [3].

Fortin et al. also addressed the issue of locoregional RT in node-positive breast cancer patients [6]. They found that in patients with ≤ 3 pN+ receiving locoregional RT the regional control was better (98% and 93% at 10 and 15 years) than in patients who received breast RT only (95% and 83%). Comparable results were reported by Woodward et al. [42].

Table 5. Multivariate analyses of variables for survival after stratification for surgery (n = 25,421). BCS: breast-conserving surgery; ER: estrogen receptor; ME: mastectomy; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; PR: progesterone receptor; RT: radiotherapy; SEER: Surveillance, Epidemiology and End Results.

Tabelle 5. Multivarianzanalysen der Variablen für die Überlebensraten nach Stratifikation gemäß Operationstechnik (n = 25 421). BCS: brusterhaltende Operation; ER: Östrogenrezeptor; ME: Mastektomie; N+ ratio: $(N_{pos}/N_{tot}) \times 100$; PR: Progesteronrezeptor; RT: Strahlentherapie; SEER: Surveillance, Epidemiology and End Results.

Variables		Hazard ratio* After ME	Confidence intervals	Hazard ratio* After BCS	Confidence intervals
Age	< 50 years	1		1	
	50–60 years	1.17	1.09–1.25	1.04	0.93–1.16
	> 60 years	2.10	1.99–2.22	1.79	1.63–1.97
Breast	Right	0.99	0.97–1.01	1.00	0.96–1.05
	Left	1		1	
Grading	1–2	0.86	0.83–0.89	0.80	0.76–0.85
	3–4	1		1	
T-stage	T1	0.82	0.81–0.84	0.79	0.76–0.83
	T2	1		1	
Quadrant	Inner	1.10	1.03–1.17	1.33	1.18–1.49
	Other	1		1	
Histology	Duct cell	1.09	1.03–1.15	1.00	0.90–1.12
	Other	1		1	
N+ ratio	≤ 20%	1		1	
	21–65%	1.52	1.45–1.59	1.51	1.38–1.66
	> 65%	2.49	2.34–2.64	2.72	2.42–3.06
ER receptor status	Negative	1.23	1.14–1.32	1.16	1.02–1.32
	Positive	1		1	
PR receptor status	Negative	1.15	1.08–1.23	1.15	1.03–1.30
	Positive	1		1	
Database	SEER no RT	1.38	1.21–1.56	1.49	1.14–1.95
	SEER with RT	1.15	1.00–1.32	1.21	0.93–1.57
	UZ Brussel	1		1	

*Hazard ratio < 1 indicates a favorable prognosis to reference (= 1)

At present, RT is not routinely used in patients with node-positive breast cancer, although it is coming into use to treat patients with ≥ 4 pN+.

In the SEER database, there is no information available why patients were not subjected to postoperative RT. Several publications state that the highest rates of RT are seen in communities close to RT centers: geographic location is an important predictor of RT use. Poverty, health insurance coverage, and older age play a less important role [1, 15, 21].

However, it is important to recognize the limitations of this study. It is a retrospective review of two separate cohorts with significant differences in the distribution of variables that confound patient outcome. In SEER, no information is available concerning adjuvant chemotherapy or hormonal treatment. However, for patients included in the UZ Brussel database, there is no bias concerning treatment: all patients received postoperative RT as standard treatment. Furthermore, patients receiving RT who were included in the SEER or UZ Brussel database had the same OS (Figure 1) and comparable multivariate analyses (Table 4).

Our results concur with a recent SEER study that analyzed radiation use and long-term survival in breast cancer patients with T1–T2 primary tumors and one to three positive axillary lymph nodes, which also found a survival advantage for patients receiving RT [2]. Analyses of retrospective data cannot account for all potential biases; our results require confirmation in randomized clinical trials, such as the ongoing MRC/EORTC SUPREMO trial which addresses the issue of post-ME RT in patients with ≤ 3 pN+ [12]. Nevertheless, the current evidence supports recommending RT in patients with ≤ 3 pN+ as a standard treatment.

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