Strahlenther Onkol
https://doi.org/10.1007/s00066-018-1343-x

ORIGINAL ARTICLE

Impact of postmastectomy radiotherapy on the outcomes of breast cancer patients with T1–2 N1 disease

An individual patient data analysis of three clinical trials

Omar Abdel-Rahman[1,2]

Received: 10 April 2018 / Accepted: 14 July 2018

Abstract

Purpose To assess the impact of postmastectomy radiotherapy (PMRT) on overall survival and relapse-free survival among breast cancer patients with T1–T2 N1 disease who received standard adjuvant systemic therapy.

Methods This is an individual patient data pooled analysis of 1053 breast cancer patients referred for adjuvant therapy in three clinical trials (BIG 02/98, BCIRG001, and BCIRG005). Overall survival was assessed according to whether or not patients received adjuvant radiotherapy through Kaplan–Meier analysis. Univariate and multivariate analyses of predictors of overall and relapse-free survival were conducted through Cox regression analysis.

Results Locoregional relapse rates (after a median follow up of 116 months) were 5.6% among patients who received adjuvant radiotherapy vs. 6.6% among patients who did not receive adjuvant radiotherapy. Actuarial 5- and 10-year locoregional relapse-free survival rates were 94 and 93%, respectively, among patients who did not receive adjuvant radiotherapy versus 95 and 92% among patients who received adjuvant radiotherapy. The following factors were associated with worse overall survival in multivariate Cox regression analysis: age < 40 years ($P < 0.0001$), T2 stage ($P = 0.004$), higher lymph node ratio ($P < 0.0001$), and negative hormone receptor status ($P < 0.0001$). Likewise, the following factors were predictive of shorter locoregional relapse-free survival: age ≤ 40 ($P < 0.0001$), no PMRT ($P = 0.034$), fluorouracil/adriamycin/cyclophosphamide (FAC) chemotherapy ($P = 0.001$), and higher T stage ($P = 0.002$).

Conclusion The current analysis does not show a beneficial impact of PMRT on overall or relapse-free survival among patients with T1–T2 N1 disease who received standard adjuvant systemic therapy. There is, however, evidence of improvement in locoregional relapse-free survival with PMRT. These findings need to be prospectively validated.

Keywords Locoregional control · Survival · Prognosis · Evidence-based medicine · Relapse

✉ Dr. Omar Abdel-Rahman, MD
omar.abdelsalam@ahs.ca, omar.abdelrhman@med.asu.edu.eg

[1] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[2] Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada

Published online: 01 August 2018

Auswirkungen der Strahlentherapie nach Mastektomie auf die Ergebnisse von Mammakarzinompatientinnen im Stadium T1–2 N1

Eine individuelle Patientendatenanalyse aus 3 klinischen Studien

Zusammenfassung

Ziel Untersuchung der Auswirkungen der Postmastektomie-Strahlentherapie (PMRT) auf das Gesamtüberleben und das rezidivfreie Überleben von Mammakarzinompatientinnen im Stadium T1–2 N1, die anschließend eine systemische adjuvante Standardtherapie erhielten.

Methoden Gepoolte individuelle Patientendatenanalyse von 1053 Mammakarzinompatientinnen mit einer adjuvanten Systemtherapie im Rahmen von drei klinischen Studien (BIG 02/98; BCIRG001, BCIRG005). Das Gesamtüberleben von Patientinnen mit und ohne adjuvante Strahlentherapie wurde mittels Kaplan-Meier-Analyse verglichen. Zur univariaten und multivariaten Analyse von unabhängigen Prädiktoren für das Gesamt- und rezidivfreie Überleben wurde eine Cox-Regression durchgeführt.

Ergebnisse In einem medianen Follow-up-Zeitraum von 116 Monaten kam es in 5,1 % aller Patientinnen mit adjuvanter Strahlentherapie zum lokoregionären Rezidiv im Vergleich zu 6,4 % der nichtbestrahlten Patientinnen. Die rezidivfreien 5-Jahres- und 10-Jahres-Überlebensraten betrugen 94 und 93 % bei Patientinnen ohne bzw. 95 und 92 % mit adjuvanter Strahlentherapie. Die folgenden Faktoren waren mit einem schlechteren Gesamtüberleben in der multivariaten Cox-Regression assoziiert: Alter < 40 Jahre ($P < 0{,}0001$), T2-Stadium ($P = 0{,}004$), höheres Lymphknotenverhältnis ($P < 0{,}0001$) und negativer Hormonrezeptorstatus ($P < 0{,}0001$). Zudem waren die folgenden Faktoren prädiktiv für ein kürzeres lokoregionäres rezidivfreies Überleben: Alter < 40 ($P < 0{,}0001$), kein PMRT ($P = 0{,}034$), „Fluorouracil/Adriamycin/Cyclophosphamide“(FAC)-Chemotherapie ($P = 0{,}001$) und höheres T-Stadium ($P = 0{,}002$).

Fazit Die aktuelle Analyse zeigt keinen positiven Einfluss der PMRT auf das Gesamt- oder rezidivfreie Überleben bei Patientinnen mit Mammakarzinom im Stadium T1–2 N1, die eine standardmäßige adjuvante Systemtherapie erhielten. Es gibt aber Hinweise auf eine Verbesserung des lokoregionalen rezidivfreien Überlebens mit PMRT. Diese Ergebnisse bedürfen jedoch einer prospektiven Evaluierung.

Schlüsselwörter Locoregionale Kontrolle · Überleben · Prognose · Rückfälle · Medizin basierend auf Fakten

Introduction

Following breast-conserving surgery, adjuvant radiotherapy is a standard evidence-based practice in almost all patients [1]. On the other hand, following mastectomy, adjuvant radiotherapy was recommended for patients with a higher risk of locoregional recurrence (including > T2 stage, >4 positive lymph nodes, or positive margins; [2]).

For patients with T1–2, N1 disease, the indication for postmastectomy radiotherapy (PMRT) is less certain [3, 4]. The majority of the studies showing potential benefit for this subset of patients were either retrospective in nature with numerous confounding factors or old prospective trials that were conducted in an era where standard adjuvant systemic therapy was not yet fully evolved [5, 6]. Given the observation that systemic therapy is an important determinant for the risk of locoregional relapse and thus for the potential benefit from adjuvant radiotherapy [1], there is a pressing need to prospectively reassess the real benefit of adjuvant radiotherapy in this subset of patients in the context of currently approved standard adjuvant systemic therapy.

The recently launched collaborative project (Project Data Sphere, PDS) allows access to the raw data of a number of practice-changing oncology trials [7]. Among the available trials in this project, there are a number of phase III trials evaluating adjuvant chemotherapy regimens for operable breast cancer. It was thus thought that assessment of the outcomes of PMRT for T1–2N1 breast cancer patients enrolled into these studies would provide an insight into the outcomes of this subset of patients in the context of effective, currently accepted adjuvant systemic therapy regimens.

Proper evaluation of the potential benefit from adjuvant radiotherapy in this setting should inform practice for this very common disease.

Objective

To assess the impact of PMRT on overall survival, relapse-free survival, and locoregional control among breast cancer patients with T1–2N1M0 disease who received standard adjuvant chemotherapy.

Methodology

Description of the study cohort

The current analysis is based on an individual patient data analysis of three phase III trials evaluating different adjuvant chemotherapy regimens for breast cancer. These three trials were chosen on the basis of availability of raw data within the PDS initiative as well as regarding the suitability of these trials to answer the primary research question. After appropriate approvals and through the PDS initiative, the data were downloaded. The three trials are NCT00174655 (BIG 02/98), NCT00688740 (BCIRG001), and NCT00312208 (BCIRG005; only the datasets of control arms were available for the three studies). The primary results of these trials were analyzed and have been published previously [8–10]. Table 1 summarized details of each of these trials. Overall, a total of 3390 patients were available from the combined dataset. Out of this combined dataset, 1053 patients with T1–T2 N1 disease who were treated with mastectomy and have complete information about radiotherapy and survival were further selected in the study cohort. Fig. 1 describes the selection process of the sub-cohort of the current study.

Data collection

The following information was obtained from each of the included datasets; age at diagnosis; body mass index, race, performance score, lymph node ratio (number of positive lymph nodes to number of examined lymph nodes), pathological T and N stage, grade, hormone receptor status (estrogen and progesterone receptors), Her2 neu status, histological subtype, whether or not adjuvant radiotherapy was administered, protocol of adjuvant chemotherapy, overall survival, vital status, relapse status, and relapse-free survival. Events of locoregional recurrence were also sought and defined as any event of ipsilateral local or regional recurrence.

In accordance with the available protocol of the included trials, all included patients have adequate organ function (including cardiac, hepatic, renal, and bone marrow functions) and all patients have good performance status. Overall survival was defined in the current analysis as "time from randomization till death" (patients were censored if they were alive at the time of database lock for each study). Relapse-free survival was defined as "time from randomization till local, regional, or distant relapse" (patients were censored if they were alive at the time of database lock or if they died without relapse). Locoregional relapse-free survival was defined as "time from randomization till local or regional relapse" (patients were censored if they were alive at the time of database lock or if they died without locoregional relapse).

Table 1 Studies included in the current pooled analysis[a]

Study	Chemotherapy regimens	Percentage of patients in the pooled analysis (%)	Study start date	Primary completion date
BCIRG001 (NCT00688740; comparator arm only)	Active Comparator: FAC 5-fluorouracil (500 mg/m^2) in combination with Adriamycin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) on day 1 every 3 weeks for 6 cycles	39.8	June 1997	January 2010
BIG 02/98 (NCT00174655; only comparator arms)	Active comparator A1 (A-CMF): Adriamycin 75 mg/m^2 i.v. day 1 q 21 days for 4 cycles, followed by CMF (C: cyclophosphamide 100 mg/m^2 orally days 1–14, M: methotrexate: 40 mg/m^2 i.v. days 1 and 8, FU; 5-fluorouracil: 600 mg/m^2) i.v. days 1 and 8, q 28 days for 3 cycles. Active comparator A2 (AC-CMF): Adriamyicn 60 mg/m^2 i.v. + cyclophosphamide 600 mg/m^2 i.v., day 1, q 21 days for 4 cycles, followed by CMF for 3 cycles	A1: 9.6 A2: 10.1	June 1998	September 2011
BCIRG005 (NCT00312208; comparator arm only)	Active comparator: AC x 4: Adriamyicn 60 mg/m^2 as an i.v. bolus in combination with cyclophosphamide 600 mg/m^2 as i.v. followed by docetaxel 100 mg/m^2 as 1 h i.v. infusion on day 1 every 3 weeks for 4 cycles	40.6	November 2001	October 2013

All the names of the drugs are for the active ingredient and not commercial names for a marketed product
HR hazard ratio, *CI* confidence interval, *FAC* fluorouracil/adriamycin/cyclophophamide, *A-CMF* adriamycin-cyclophosphamide/methotrexate/fluorouracil, *AC-CMF* adriamycin/cyclophosphamide-cyclophosphamide/methotrexate/fluorouracil, *AC-docetaxel* adriamycin/cyclophosphamide-docetaxel
[a]Adjuvant hormonal therapy and trastuzumab were allowed according to local guidelines in each institute

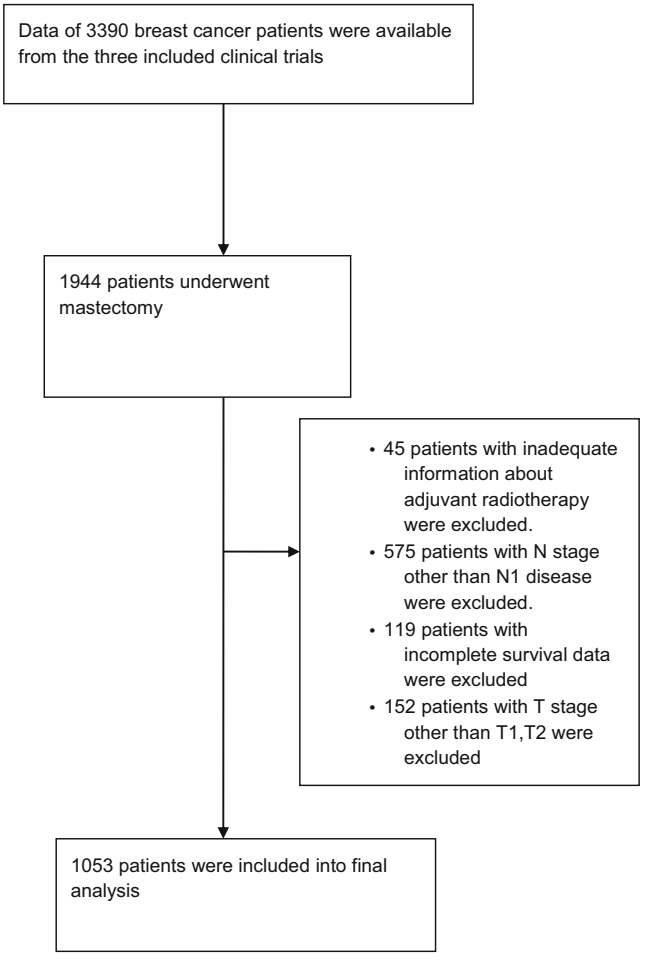

Fig. 1 Flowchart for the selection process of study cohort

Statistical considerations

Baseline characteristics of included patients were detailed through descriptive statistics and chi-squared testing was used to differentiate baseline characteristics of patients who received versus those who did not receive adjuvant radiotherapy. The probability of overall survival was assessed according to whether or not patients received adjuvant radiotherapy through Kaplan–Meier analysis and log-rank testing.

Univariate and multivariate analyses of predictors of overall, relapse-free, and locoregional relapse-free survival were conducted through Cox regression analysis. The following variables were examined for their potential impact on overall and relapse-free survival: age, menopause, T stage, lymph node ratio, hormone-receptor status, adjuvant radiotherapy, and chemotherapy protocol. Variables with a statistically significant *P*-value ($P < 0.05$) in the univariate analysis were included in the multivariate analysis. Proportional hazard assumption was assessed graphically for the three endpoints (overall, relapse-free, and locoregional relapse-free).

Although patients within this analysis were derived from randomized studies, those patients were not randomized for the endpoint of assessing the impact of PMRT. Unbalanced baseline characteristics could have thus led to some sort of selection bias and, accordingly, this might have influenced the decision to administer PMRT. The propensity score matching approach was thus additionally employed in this analysis in order to account for this potential limitation [11]. It is defined in this analysis as the probability of being assigned to PMRT or no PMRT groups given the baseline characteristics. In the calculation of the propensity scores, the following baseline covariates were considered in the logistic regression model: age at diagnosis, T stage, grade, hormone receptor status, and type of chemotherapy administered. These factors were chosen on the basis of their known prognostic relevance for the outcomes of early breast cancer patients. Number of matches per observation was established at 1.

A two-tailed *P*-value < 0.05 was counted as statistically significant. Statistical analyses were evaluated using SPSS Statistics 20.0 (IBM, Armonk, NY, USA) and STATA software 14.0 (STATAcorp, TX, USA).

Results

Most patients have an age in the range of 40–69 years (85.8%) and Caucasian race represents the majority of cases with known race (53.5%). The majority of the patients have a T2 stage (59.8%), ductal carcinoma histology (81.5%), and hormone receptor-positive disease (71.4%). Only a minor percentage of patients have a G3 disease (35.5%). Premenopausal patients represent 51.9% of the study cohort. All patients were treated with mastectomy and adjuvant chemotherapy. 53.9% of patients received adjuvant radiotherapy while 46.1% did not receive adjuvant radiotherapy. Median number of resected lymph nodes is 10 lymph nodes (range: 2–46). 750 patients (71.2%) have complete phenotype information (hormone receptor and Her2 status). Among those 750 patients, 508 patients have hormone receptor +ve/Her2 –ve disease, 144 patients have triple negative disease, 44 patients have hormone receptor –ve/Her2 +ve disease, and 54 patients have hormone receptor +ve/Her2 +ve disease. In the majority of patients who received adjuvant radiotherapy, this was conventionally fractionated (1.8–2 Gy/fraction; 25 fractions). Among patients who received PMRT, 397 patients (69.8%) received supraclavicular (± axillary) radiotherapy and 113 patients (19.8%) received internal mammary radiotherapy. All patients with known margin status (634 patients) have negative margins. Additional systemic therapies (e.g., endocrine

Table 2 Baseline characteristics of included patients in the cohort (1053 patients)

Parameter	Patients treated with PMRT (568 Patients)	Patients not treated with PMRT (485 patients)	*P*-value
Age			
<40 years	86 (15.1%)	57 (11.8%)	0.223
40–69 years	479 (84.3%)	424 (87.4%)	
≥70 years	2 (0.4%)	4 (0.8%)	
Missing	1 (0.2%)	–	
Race			
Caucasian	357 (62.9%)	206 (42.5%)	<0.0001
Others	22 (3.9%)	8 (1.6%)	
Missing	189 (33.3%)	271 (55.9%)	
Karnofsky performance score			
80	14 (2.5%)	7 (1.4%)	0.376
90	103 (18.1%)	80 (16.5%)	
100	451 (79.4%)	398 (82.1%)	
Body mass index			
Mean (range)	26.6 (14.3–41.6)	26.2 (15.2–45)	0.176
Missing	20	51	
Menopausal status			
Premenopausal	288 (50.7%)	258 (53.2%)	0.538
Postmenopausal	205 (36.1%)	173 (35.7%)	
Missing	75 (13.1%)	54 (11.1%)	
T stage			
T1	228 (40.1%)	195 (40.2%)	0.983
T2	340 (59.9%)	290 (59.8%)	
Lymph node ratio			
Mean (range)	0.26 (0.02–1)	0.17 (0.02–1)	<0.0001
Missing	0	0	
Grade			
G1	81 (14.3%)	47 (9.7%)	<0.0001
G2	235 (41.4%)	209 (43.1%)	
G3	213 (37.5%)	161 (33.2%)	
Missing	39 (6.9%)	68 (14%)	
Hormone receptor			
ER and/or PR +ve	407 (71.7%)	345 (71.1%)	0.719
Both ER/PR –ve	147 (25.9%)	124 (25.6%)	
Missing	14 (2.5%)	16 (3.3%)	
Her2 neu			
Positive	64 (11.3%)	34 (7%)	0.001
Negative	337 (59.4%)	339 (69.9%)	
Missing	167 (29.4%)	112 (23.1%)	
Histological subtype			
Invasive ductal carcinoma	476 (83.8%)	382 (78.8%)	0.003
Invasive lobular carcinoma	50 (8.8%)	56 (11.5%)	
Others	21 (3.7%)	38 (7.8%)	
Missing	21 (3.7%)	9 (1.9%)	
Laterality			
Right	144 (25.4%)	177 (36.5%)	<0.0001
Left	127 (22.4%)	186 (38.4%)	
Missing	297 (52.3%)	122 (25.2%)	

[a]Cases with $P < 0.0001$ were reported as such because the software does not produce more precise *P*-values

therapies) were administered—if indicated—as per institutional guidelines.

Comparing patients who received versus those who did not receive adjuvant radiotherapy, there was no difference in age ($P=0.223$), performance status ($P=0.376$), menopausal status ($P=0.538$), T stage ($P=0.983$), body mass index ($P=0.176$), or hormone receptor status ($P=0.719$). On the other hand, there was significant difference in race (more Caucasian patients receive PMRT; $P<0.0001$), lymph node ratio (higher ratio in patients receiving radiotherapy; $P<0.0001$), and histological subtype (more ductal carcinoma patients receive PMRT; $P=0.003$). Locoregional relapse rates were 5.6% (32 patients) among patients who received adjuvant radiotherapy vs. 6.6% (32 patients) among patients who did not receive adjuvant radiotherapy. Actuarial 5 and 10-year locoregional relapse-free survival rates were 94 and 93%, respectively, among patients who did not receive adjuvant radiotherapy versus 95 and 92% among patients who received adjuvant radiotherapy. Table 2 provides details of baseline characteristics in both groups of patients. Median follow up for the entire cohort: 116 months (range: 1.37–148).

Survival outcomes according to PMRT

Kaplan–Meier analysis of overall survival according to PMRT was conducted. Apparently, patients who did not receive PMRT seem to have better overall survival ($P=0.042$; Fig. 2). Among patients with complete information about hormone receptors/Her2 status, an additional Kaplan–Meier analysis of overall survival according to PMRT was conducted for different phenotypic subsets of patients. PMRT did not affect overall survival among all subtypes of breast cancer (triple negative, luminal, and Her2 over-expressed subtypes; data not shown).

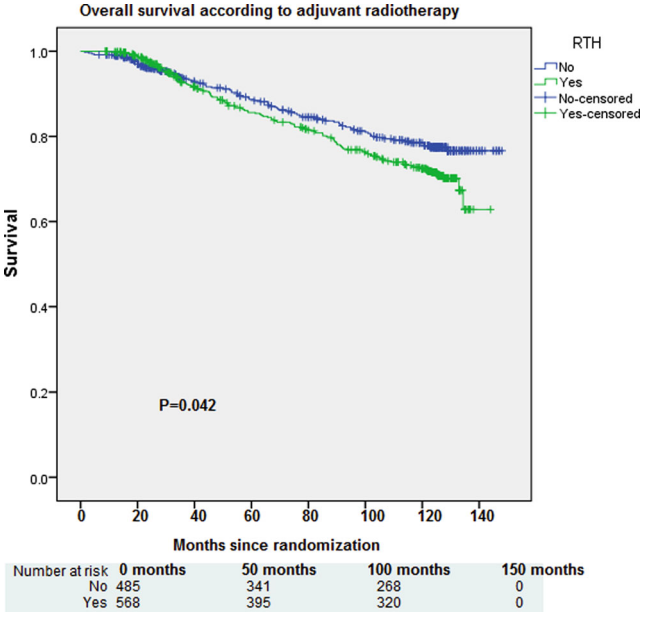

Fig. 2 Kaplan–Meier curve for overall survival according to receipt or not of adjuvant radiotherapy. *RTH* radiotherapy

Table 3 Multivariate Cox regression analysis for factors predicting overall survival

Parameters	HR (95% CI)	*P*-value
Age		
<40	Reference	–
40–69	0.520 (0.395–0.685)	<0.0001
≥70	0.747 (0.229–2.432)	0.628
Radiotherapy		
No	Reference	0.740
Yes	0.953 (0.716–1.268)	
T stage		
T2	Reference	0.004
T1	0.656 (0.494–0.872)	
Hormone receptor		
Negative	Reference	<0.0001
Positive	0.557 (0.422–0.736)	
Lymph node ratio		
(Continuous)	5.372 (3.036–9.505)	<0.0001

HR hazard ratio, *CI* confidence interval, *FAC* fluorouracil/adriamycin/cyclophophamide, *A-CMF* adriamycin-cyclophosphamide/methotrexate/fluorouracil, *AC-CMF* adriamycin/cyclophosphamide-cyclophosphamide/methotrexate/fluorouracil, *AC-docetaxel* adriamycin/cyclophosphamide-docetaxel

[a]Cases with $P<0.0001$ were reported as such because the software does not produce more precise *P* values

Additional treatment effect estimation (for overall survival) through propensity score matching was conducted incorporating the following factors besides PMRT: age at diagnosis, T stage, hormone receptor status, grade, and type of chemotherapy administered. According to this additional analysis, PMRT did not affect the risk of death compared to no PMRT (coefficient: 0.018; 95% CI: –0.07 to 0.106; $P=0.688$).

In univariate Cox regression analysis, the following factors were significant for overall survival ($P<0.05$): age, T stage, lymph node ratio, hormone receptor status, and adjuvant radiotherapy. When these factors were included in the multivariate analysis, the following factors were associated with worse overall survival: age < 40 years ($P<0.0001$), T2 stage ($P=0.004$), higher lymph node ratio ($P<0.0001$), and negative hormone receptor status ($P<0.0001$; Table 3). Adjuvant radiotherapy was not associated with better overall survival ($P=0.740$).

Likewise, in univariate analysis for relapse-free survival, the following factors were significant ($P<0.05$): age, T stage, lymph node ratio, hormone receptor status, chemotherapy protocol, and adjuvant radiotherapy. When these factors were included in the multivariate analysis, the following factors were associated with worse relapse-free

Table 4 Multivariate Cox regression analysis for factors predicting relapse-free survival

Parameters	HR (95% CI)	*P*-value
Age		
<40	Reference	–
40–69	0.364 (0.261–0.509)	<0.0001
≥70	0.182 (0.025–1.327)	0.093
Radiotherapy		
Yes	Reference	0.970
No	0.994 (0.728–1.358)	
Chemotherapy agents		
A-CMF	Reference	–
AC-CMF	0.943 (0.190–4.676)	0.943
AC-docetaxel	0.988 (0.302–3.237)	0.984
FAC	3.462 (1.075–11.144)	0.037
T stage		
T2	Reference	<0.0001
T1	0.550 (0.406–0.747)	
Hormone receptor		
Negative	Reference	0.104
Positive	0.778 (0.575–1.053)	
Lymph node ratio		
(Continuous)	2.660 (1.307–5.414)	0.007

HR hazard ratio, *CI* confidence interval, *FAC* fluorouracil/adriamycin/cyclophophamide, *A-CMF* adriamycin-cyclophosphamide/methotrexate/fluorouracil, *AC-CMF* adriamycin/cyclophosphamide-cyclophosphamide/methotrexate/fluorouracil, *AC-docetaxel* adriamycin/cyclophosphamide-docetaxel

[a]Cases with $P<0.0001$ were reported as such because the software does not produce more precise *P* values

Table 5 Multivariate Cox regression analysis for factors predicting locoregional relapse-free survival

Parameters	HR (95% CI)	*P*-value
Age		
<40	Reference	<0.0001
≥40	0.277 (0.161–0.476)	
Radiotherapy		
Yes	Reference	0.034
No	1.750 (1.043–2.938)	
Chemotherapy agents		
FAC	Reference	–
A-CMF	Coefficients did not converge[b]	0.965
AC-CMF	Coefficients did not converge[b]	0.965
AC-docetaxel	0.347 (0.182–0.661)	0.001
T stage		
T2	Reference	0.002
T1	0.415 (0.235–0.733)	
Hormone receptor		
Negative	Reference	0.217
Positive	0.720 (0.427–1.213)	
Lymph node ratio		
(Continuous)	1.346 (0.328–5.528)	0.680

HR hazard ratio, *CI* confidence interval, *FAC* fluorouracil/adriamycin/cyclophophamide, *A-CMF* adriamycin-cyclophosphamide/methotrexate/fluorouracil, *AC-CMF* adriamycin/cyclophosphamide-cyclophosphamide/methotrexate/fluorouracil, *AC-docetaxel* adriamycin/cyclophosphamide-docetaxel

[a]Cases with $P<0.0001$ were reported as such because the software does not produce more precise *P* values

[b]Coefficients did not converge and further models cannot be fitted for this parameter

survival: age < 40 years ($P<0.0001$), T2 stage ($P<0.0001$), higher lymph node ratio ($P=0.007$), and FAC chemotherapy protocol ($P=0.037$; Table 4). Adjuvant radiotherapy was, however, not associated with better relapse-free survival in the multivariate analysis ($P=0.970$). The above multivariate analysis was repeated after including an interaction between surgery to chemotherapy interval and hormone receptor status, and this did not show any benefit for adjuvant radiotherapy either ($P=0.989$).

The impact of adjuvant radiotherapy on locoregional relapse-free survival was further assessed in a multivariate Cox regression analysis incorporating age, T stage, lymph node ratio, hormone receptor status, and chemotherapy protocol (i.e., the factors which were significant for relapse-free survival in univariate analysis). In this multivariate analysis, the following factors were predictive of shorter locoregional relapse-free survival: age ≤ 40 ($P<0.0001$), no PMRT ($P=0.034$), FAC chemotherapy ($P=0.001$), and higher T stage ($P=0.002$; Table 5).

Discussion

The current study provides an assessment of the impact of PMRT on the outcomes of patients with T1–T2 N1 disease treated with standard adjuvant systemic therapy. It suggested that—within the context of standard adjuvant systemic therapy—administration of adjuvant radiotherapy does not seem to improve overall or relapse-free survival. There is, however, evidence of improvement in locoregional relapse-free survival with PMRT. This indication needs to be thoroughly reconsidered and this finding needs to be prospectively validated.

The current analysis is not in line with a previous retrospective study suggesting better outcomes of patients with T1–T2 N1 disease treated with PMRT [12]. However, the current analysis is methodologically different, given that it includes a pooled analysis of individual patient data across a number of controlled clinical trials with sufficient follow-up (compared to previous retrospective studies).

The current analysis is not in line with the previously published Danish Breast Cancer Cooperative Group 82b and 82c trials (which showed that the addition of PMRT

prolongs survival) [13, 14]. However, the patient population is different in both trials compared to the current analysis (in both Danish studies, a considerable proportion of patients have T3/4 and/or N2/3 disease). Although a subsequent subgroup analysis of the two Danish studies suggested that the benefit for patients with N1 disease is similar to the benefit for patients with N2–3 disease, the patient population in this subgroup analysis received suboptimal systemic therapy by current standards (CMF for premenopausal women and 1 year of tamoxifen for postmenopausal women) [15]. Thus, these results cannot be compared to the results of the current analysis where patients received full-course standard adjuvant systemic therapy. Consistent with this assumption is the observation that the absolute risk reduction of locoregional relapse for N1 patients (because of adjuvant radiotherapy) in the subgroup analysis of the two Danish studies was 20% vs. only 1.3% in the current analysis. This confirms the hypothesis that more effective adjuvant systemic therapy in the current analysis decreased the probability of locoregional relapse and thus minimized the potential benefit of adjuvant radiotherapy.

Similarly, there are differences between the current analysis and the previously published British Columbia study which suggested a morality benefit for PMRT [5]. The study population of the British Columbia study incorporated T1–4 N1–3 patients. Moreover, the study was conducted from 1979 to 1986, which casts doubt about the efficacy of adjuvant systemic therapy used for those patients.

Likewise, the results of the current study are not in line with the previously published Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis which showed that PMRT reduces breast cancer mortality among women with one to three positive axillary lymph nodes [6]. However, it has to be noted that patients in this pooled analysis were treated between 1964 and 1986, where adjuvant systemic therapy protocols were not standardized and cannot be compared to the standard systemic therapy regimens used in the current analysis. Moreover, patients in the EBCTCG pooled analysis have T1–4 disease (not T1–2 disease like in the current analysis). Additionally, hormone receptor status was not known in a considerable proportion of the patients in the EBCTCG analysis.

The current study has, however, some limitations and these need to be acknowledged. Data about additional factors which might contribute to the risk of locoregional recurrence following mastectomy (e.g., lymphovascular space invasion) [16] were not adequately covered in the pooled data of these trials. Moreover, full details about the volume and fractionation of radiation therapy are not provided (given that the primary focus of all of the included studies was on the systemic therapy used). Additionally, the current analysis is a secondary analysis and not the primary research question of the three studies (i.e., patients were not randomized between PMRT and no PMRT). This might be a source of confounding and for this purpose, multivariate Cox regression analysis as well as propensity score matching were employed to account for this potential confounding. Another limitation in the current analysis might be the lack of information about smoking in the majority of patients (which has been shown in a recent study to increase the risk of relapse of breast cancer) [17].

It must also be noted that all patients included in the current analysis received adjuvant anthracycline-based chemotherapy. Thus, the results of the current study cannot be extended to T1–2N1 patients who are planned for adjuvant endocrine therapy alone. Additional studies are needed to elucidate the role of PMRT among those patients.

The median number of resected lymph nodes is 10 (range: 2–46) in the current study. It is not clear from the available protocols/datasets of included studies if some patients were treated with sentinel lymph node biopsy or not. This is a potential confounder that should be taken into consideration when interpreting the results of the current analysis.

In order to interpret properly the overall lower rates of locoregional recurrences in the current analysis (compared to previous prospective studies), additional factors (other than improved systemic therapy) might be considered. These include more optimal surgical procedures which might have contributed to lower rates of subsequent locoregional relapses.

Consistent with previous retrospective studies, younger age, T2 stage, hormone receptor-negative status, and higher lymph node ratio may be associated with a higher risk of relapse and mortality [18, 19]. However, the current analysis suggested that PMRT might not be the optimal way to tackle that increasing risk. The data from this analysis should be viewed as hypothesis generating but need to be confirmed by future phase III trials.

Recently, a subset analysis of the BIG 02-98 study was published evaluating a similar question to the one posed by the current study [20]. However, this study incorporated all mastectomy-treated patients included in BIG 2-98 study (both experimental and comparator arms). The PDS datasets from which the current analysis was derived include only patients in the comparator arms. Thus, the results of the two studies cannot be compared.

Interestingly, PMRT was associated with worse overall survival in Kaplan–Meier analysis. However, this finding was not replicated in multivariate Cox regression analysis. This indicates that worse outcomes among radiotherapy-treated patients might be related to adverse clinicopathological characteristics rather than radiotherapy itself.

In conclusion, the current analysis does not suggest a beneficial impact for PMRT on overall or relapse-free survival among patients with T1–T2 N1 disease who re-

ceived standard adjuvant systemic therapy. There is, however, evidence of improvement in locoregional relapse-free survival with PMRT. The study additionally provides evidence that the frequency of locoregional recurrence after mastectomy is considerably low in this good prognostic subset of patients treated with contemporary systemic therapies. Further prospective validation of these findings needs to be performed. The indications for PMRT need to be thoroughly reassessed in the context of currently available standard adjuvant systemic therapy.

Acknowledgements This publication is based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC, nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this publication. The datasets were downloaded from the project data sphere platform after obtaining all appropriate relevant approvals.

Compliance with ethical guidelines

Conflict of interest O. Abdel-Rahman declares that he has no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E et al (2015) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Suppl 5):v8–v30
2. Salerno KE (2017) NCCN guidelines update: evolving radiation therapy recommendations for breast cancer. J Natl Compr Canc Netw 15(5s):682–684
3. Gradishar W, Salerno KE (2016) NCCN guidelines update: breast cancer. J Natl Compr Canc Netw 14(5 Suppl):641–644
4. Wenz F, Sperk E, Budach W, Dunst J, Feyer P, Fietkau R et al (2014) DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer. Strahlenther Onkol 190(8):705–714
5. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE et al (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337(14):956–962
6. EBCTCG (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 383(9935):2127–2135
7. CEO Life Sciences Consortium (2014) Project Data Sphere. https://www.projectdatasphere.org/projectdatasphere/html/home. Accessed 7 Oct 2017
8. Fernandez-Cuesta L, Oakman C, Falagan-Lotsch P, Smoth KS, Quinaux E, Buyse M et al (2012) Prognostic and predictive value of TP53 mutations in node-positive breast cancer patients treated with anthracycline- or anthracycline/taxane-based adjuvant therapy: results from the BIG 02-98 phase III trial. Breast Cancer Res 14(3):R70
9. Mackey JR, Martin M, Pienkowski T, Rolski J, Guastalla JP, Sami A et al (2013) Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol 14(1):72–80
10. Eiermann W, Pienkowski T, Crown J, Sadeghi S, Martin M, Chan A et al (2011) Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. J Clin Oncol 29(29):3877–3884
11. Alberto A, Imbens GW (2006) Large sample properties of matching estimators for average treatment effects. Econometrica 74(1): 235–267
12. Korah MP, Sener SF, Tripathy D (2013) The impact of postmastectomy radiation therapy in intermediate-risk breast cancer patients with limited axillary disease. Int J Radiat Oncol Biol Phys 87(2):S230
13. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F et al (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 337(14):949–955
14. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M et al (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353(9165):1641–1648
15. Overgaard M, Nielsen HM, Overgaard J (2007) Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 82(3):247–253
16. Su Y-L, Li S-H, Chen Y-Y, Chen H-C, Tang Y, Huang C-H et al (2014) Post-mastectomy radiotherapy benefits subgroups of breast cancer patients with T1–2 tumor and 1–3 axillary lymph node(s) metastasis. Radiol Oncol 48(3):314–322
17. Abdel-Rahman O, Cheung WY (2018) Impact of smoking history on the outcomes of women with early-stage breast cancer: a secondary analysis of a randomized study. Med Oncol 35(5):68
18. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E (2005) Selecting breast cancer patients with T1–T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 61(5):1337–1347
19. Cheng JC, Chen CM, Liu MC, Tsou MH, Yang PS, Jian JJ et al (2002) Locoregional failure of postmastectomy patients with 1–3 positive axillary lymph nodes without adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 52(4):980–988
20. Zeidan YH, Habib JG, Ameye L, Paesmans M, de Azambuja E, Gelber RD et al (2018) Postmastectomy Radiation Therapy in Women with T1–T2 Tumors and 1 to 3 Positive Lymph Nodes: Analysis of the Breast International Group 02-98 Trial. Int J Radiat Oncol Biol Phys 101(2):316–324