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Indications for boost irradiation after quadrantectomy for early breast cancer

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Introduction. Controversies still exist on boost irradiation after quadrantectomy for early breast cancer.
Material and methods. A retrospective study on 341 pTNM I-II staged (<3 cm) patients aimed to evaluate boost irradiation effect mainly upon local tumour control, measured by Recurrence Free Survival - (RFS) and consequently to Disease Free Survival (DFS). Whole breast, scar and chest wall were irradiated by 50 Gy telecobalttherapy in all patients and 224 of them were chosen to receive additional 10 Gy to the tumour bed.
Results and conclusion. No significant difference was registered in 10 years RFS (96%) in 224 patients receiving 10 Gy boost irradiation, compared to 95% RFS of the 117 patients irradiated with 50 Gy to the whole breast. DFS was 89% at 10th year and did not differ in both groups. The local relapse rate at 10th year was among the lowest figures reported – 3.4% for boost group and 3.6% for no-boost group. Proportional hazard Cox model reveal a high-risk group for local recurrence that might benefit from boost irradiation (tumour size 2.1-3 cm; G3, negatives steroid receptors). In our practice, patients developing such characteristics have indications for boost irradiation.

Radioterapia u chorych z wczesnym rakiem sutka po kwadrantektomii – wskazania do podwyższenia dawki na wydzielone pole („boost”)

Wstęp. Istnieją kontrowersje dotyczące stosowania podwyższonej dawki na wydzielone pole („boost") u chorych po kwadrantektomii, wykonanej we wczesnym raku sutka.
Materiał i metody. Przeprowadzono retrospektywną analizę 341 chorych z rakiem sutka w stadium pTNM I/II (guz poniżej 3 cm średnicy) po kwadrantektomii pod kątem oceny stosowania podwyższonej dawki na wydzielone pole („boost”) w celu zapewnienia kontroli miejscowej, mierzonej jako czas przeżycia bez wznowy (Recurrence Free Survival, RFS) i w efekcie, czas przeżycia bez choroby (Disease Free Survival, DFS). Podawano dawkę 50 Gy (techniką teleradioterapii kobaltowej) na całą pierś, bliznę pooperacyjną i ścianę klatki piersiowej, a u 224 chorych dodatkowo "boost" 10 Gy, skierowany na lożę po guzie.
Wyniki i wnioski. W ciągu 10 lat obserwacji nie stwierdzono statystycznie znamiennej różnicy w zakresie odsetka RFS: 96% w grupie 224 chorych, które otrzymały "boost" i 95% w grupie 117 chorych, które nie otrzymały „boostu”. Odsetek DFS był w 10-tym roku obserwacji taki sam w obu grupach – tj. 89%. Odsetek wznów miejscowych po 10 latach należał do najniższych opisywanych w literaturze – 3,4% w grupie, która otrzymała „boost” i 3,6% chorych w grupie, która nie otrzymała „boostu”. Analiza wieloczynnikowa metodą Coxa pozwoliła wyłonić grupę chorych o podwyższonym ryzyku wznowy miejscowej, które mogłyby odnieść wyraźną korzyść z naświetlania, z zastosowaniem podwyższonej dawki na wydzielone pole. Są to chore, u których rozmiary guza osiągają 2,1-3 cm, nowotwór zaś wykazuje cechę G3 i nie posiada receptorów steroidowych.

Key words: early breast cancer, quadrantectomy, boost irradiation
Słowa kluczowe: wczesny rak sutka, kwadrantektomia, napromienianie z podwyższeniem dawki na wydzielone pole

Introduction

It is a standard practice to recommend radiotherapy (RT) to residual breast after breast conserving surgery (BCS). Recurrence rate at the remaining breast near to the tumour after BCS ranges between 43-9% without radiotherapy [1-5]. The difference depends on structure of evaluated subgroups and different term of the follow- up.

Now, data from seven randomized trials have shown a substantial improvement in local tumour control in irradiated patients after BCS compared to non-irradiated on average from 27% to 7% at 10 years [6-7]. Moreover, there is a well-established practice in most European countries and in US to give an additional dose as a "boost" to the tumour area. The rationale for such increase of

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the dose is based on a theory that a lower recurrence rate will be achieved without severe risk of local radiation complications [8-9].

The need for dose boost is questioned, if operative margins are clear from tumour cells after type of surgery as quandartectomy or expanded sectoral resection [10-13]. Therefore, a definition of a risk group that might benefit from high dose irradiation is very important.

Our study aimed to analyse the benefit of 10 Gy boost given by telecobalttherapy after quadrantectomy in early (>3 cm) breast cancer.

Material and methods

In the period 1987-1997, 345 patients with pTNM Stage I and Stage II (>3 cm) breast cancer were treated at the Department of Radiotherapy, University Hospital "Queen Giovanna", Sofia. The median follow-up was 6.5 years, ranging from 1.5 to 11.5 years. All patients underwent quadrantectomy with axillary dissection as BCS. Adjuvant chemotherapy and hormonal therapy were added if there were indications for it.

One month after the operation patients were subjected to ^{60}Co external beam RT. The clinical target volume (CTV-1) in pN0 patients included the breast with the operative scar and the underlying chest wall; they received a total dose (TD) of 50 Gy. Patients with pNx (below dissected 7 negative axillary lymph nodes) and pN1 were irradiated with the extra CTV volume which included the regional nodal areas (axillary, ipsilateral mammary, supraclavicular) up to a TD of 50 Gy (CTV-2). 245 chosen at the descretion of a physician patients (66%) received 10 Gy extra beam boost to the tumor bed. Clinical characteristics of boost and non-boost group are shown on Table I. No significant differences were calculated between both arms.

Recurrence-free survival was evaluated as a primary clinical end-point. We have chosen a Disease-Free Survival to be a secondary end-point as a common criterion for local and distant failures. Survival analysis was calculated by Kaplan Mayer method. The level of significance was set as $p<0.05$. All p values were two-tailed. A benefit from boost radiation according to some prognostic factors was tested by Cox regression model. Following variables were studied in both groups: pT, G, steroid receptors, volume of axillary dissection (under or over 7 dissected lymph nodes). Statistical analysis was computed by standard PC package from Statistica [14]

Results

Boost irradiation and local tumour control. Recurrence-free survival

Detailed characteristics and treatment of the patients with local recurrences are shown on Table II. Twelve cases (3.5%) with local recurrence were registered in both groups. All recurrences were developed 1-5.5 years after RT and 96% of patients a remained local tumour free. There were no relapses registered in the regional lymph nodes areas. Nine of the local relapses are marginal. They were located less then 3 cm from the operative scar, that is very near to the primary tumor bed. Three skin relapses were registered into the radiation field. High-risk histological characteristics were presented in both groups with relapses. Ten out of twelve patients with local relapse are alive. Radical mastectomy alone or combined with adjuvant chemotherapy was carried out as a salvage treatment. Two of the recurred patients developed pulmonary and hepatic distant metastases and later succumbed.

Eight recurrences (3.6%) were registered In the boost group after delivering an extra boost dose of 10 Gy to 50 Gy at the whole breast. The remaining four relapses were observed in non – boost group (3.4%). Obviously, the boost irradiation after quadrantectomy does not show higher local tumour control.

Figure 1 presents comparative Recurrence Free Survival (RFS) in boost and no- boost groups. Ten years RFS is between 96-95% with no difference between two curves (log rank $p=0.56$).

Figure 2 shows a comparative RFS in additionally selected group of pT2 patients with tumour size between 2.1 and 3 cm. No significant difference ($p=0.39$) was registered in the first group that received a higher dose given as a boost; nevertheless 91.6% did not recurred in comparison with 81% in the second group.

Further analysis was made in patients selection having two risk parameters: tumour size 2.1-3cm and low tumour differentiation – G3. The numbers of observations became smaller and smaller (18 in the boost and 19 in the no-boost group) and no difference in RFS were detected Figure 3 ($p=0.8$). However, it seems that parameter G3 further declines RFS in both groups (86% and 82%).

Table II. Clinical, pathological and treatment characteristics of patients with local relapse

Boost	Age	Histology	pT (cm)	pN	G	LTC (years)	Ca *in situ*	Tumour necrosis	Micro -calcificates	Tumour metaplasia	Vessel invasion	Distant metastases	Hormone therapy	Chemo -therapy	Outcome
yes	38	Gelatinous	2	N1	G2	2.8	yes	no	yes	no	no	no	yes	yes	alive
yes	54	Invas. ductal	1	N0	G2	1.5	no	yes	no	no	yes	no	no	no	alive
yes	55	Invas. ductal	3	N0	G3	1.4	no	no	no	yes	no	yes	yes	no	dead
yes	57	Invas. lobular	1	N0	Gx	1.5	no	no	no	no	no	no	yes	yes	alive
yes	44	Invas. ductal.	2	N1	G3	1.0	no	no	yes	no	no	no	yes	yes	alive
yes	54	Invas. ductal.	3	N1	G3	1.5	no	no	yes	no	no	no	yes	yes	alive
yes	54	Invas. ductal.	3	N1	G3	1.5	no	no	yes	no	no	no	no	yes	alive
yes	35	Invas. ductal.	1	N1	Gx	5.5	no	no	no	no	no	no	yes	yes	alive
no	47	Gelatinous	2	N1	G1	2.9	no	no	no	no	no	no	yes	yes	alive
no	51	Invas. ductal	3	N1	Gx	5.0	no	no	no	no	no	yes	yes	yes	dead
no	40	Invas. lobular	1	N0	Gx	2.0	no	no	no	no	no	no	yes	no	alive
no	39	Invas. ductal	2	N0	Gx	1.0	no	no	no	no	no	no	no	no	alive

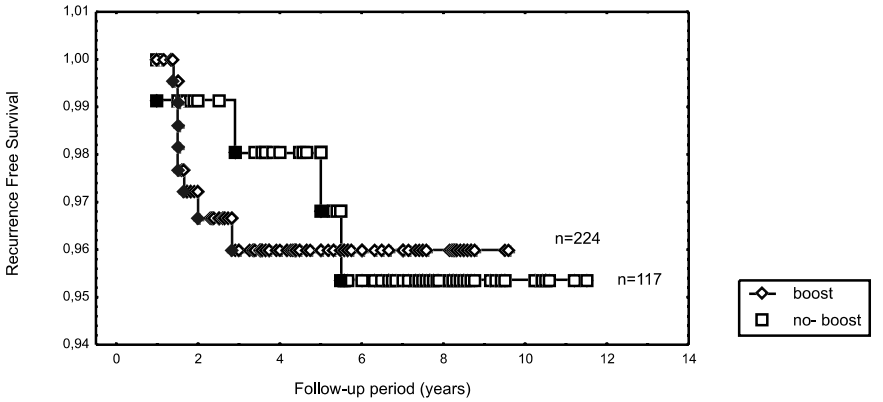

Figure 1. Recurrence Free Survival of patients with early breast cancer after quadrantectomy and radiotherapy for boost and no-boost group

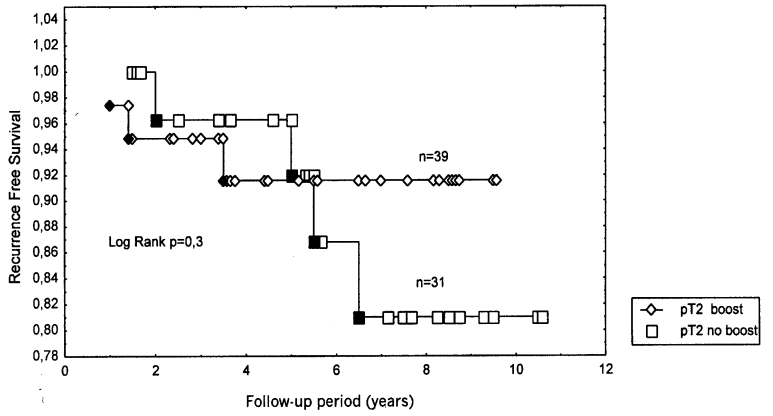

Figure 2. Recurrence Free Survival in boost and no-boost group, with tumour size between 2.1 and 3.0 cm (pT2)

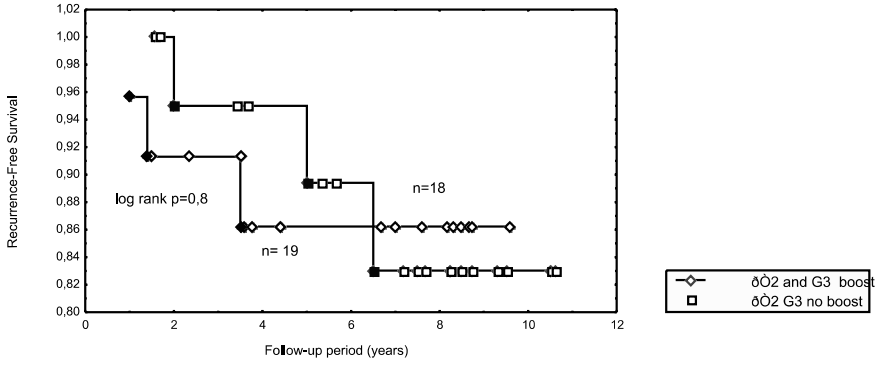

Figure 3. Recurrence Free Survival in pT2 (2.1-3.0 cm) and G3 boost and no-boost group

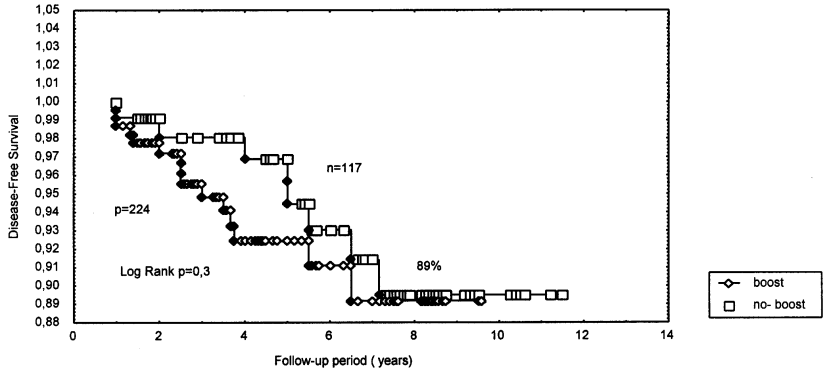

Figure 4. Disease Free Survival of patients with early breast cancer after quadrantectomy and radiotherapy for boost and no-boost group

Disease free survival (DFS)

Two of the recurred patients developed pulmonary and hepatic distant metastases and later succumbed. They belong to each of the compared groups. DFS is presented on Figure 4. Again, no difference in DFS was detected in two investigated patients groups reaching 89% at 10th years.

Discussion

Our study include a substantial number of patients: 117 cases whose remaining breast was irradiated up to TD 50 Gy and 224 patients with additional 10 Gy boost irradiation. Both groups were balanced according to patient, tumour and treatment characteristics (Table I).

Table I. Patients, tumour and treatment characteristics in both groups

Parameters	Boost group		No- boost group		P
	N	%	N	%	
All	224	65.7	117	34.3	
Age (years)					
>30	4	18	1	1.0	0.82
31-40	23	10.3	25	21.4	0.19
41-50	81	36.0	34	29.0	0.26
51-60	65	29.0	32	27.4	0.84
<60	51	22.8	25	21.4	0.92
Histology					
Invasive ductal	174	77.7	94	80.3	0.7
Invasive lobular	27	12.0	14	12.0	1.0
Others	23	10.3	9	7.7	0.8
High risk parameters					
pT2 /(2.1-3 cm)	39	17.5	31	26.5	0.36
G3	35	15.6	15	12.8	0.78
Microcalcificates	11	5.0	4	3.4	0.93
Comedo structures	7	3.0	4	3.4	0.93
Lymph vessel invasion	2	1.0	2	1.7	0.95
Venous vessel invasion	5	2.2	1	1.0	0.91
Tumour necrosis	6	2.7	0	0	0.39
Tumour metaplasia	3	1.3	0	0	
EIDC *in situ ductale*	2	1	1	1	
EIDC *in situ lobulare*	4	1.8	1	1	
Steroid receptors negative	56	25.0	18	15.4	0.38
Hormonal therapy	160	72.0	81	70.0	0.74
Adjuvant chemotherapy	68	30.0	23	20.0	0.35

The 10-survival analysis demonstrates significant difference neither in RFS nor in DFS between boost and no-boost arms. Our 10-years long-term results reveal the good level of Bulgarian oncological practice in early breast cancer ranking them among the best survival results (96-95% RFS and 89% DFS) [5, 6].

The numbers of observation event in our study – 12 cases with local relapses after radiotherapy – were too small to prove any difference, if it exists. Only 4 out of 117 patients, receiving 50 Gy developed local recurrences. Similarly, 8 out of 224 patients showed local relapse despite of 60 Gy administered by telecobalttherapy. Zissiadis and al. [15] reported no influence on LTC at 5 years in 78% of his patients treated by quadrantectomy and additional boost irradiation. Similar conclusion was made in NSABP-06 trial [16]. Only 8% of local relapses were registered at 5 years without boost irradiation.

Later, two large randomised trials investigated the benefit after boost irradiation. The results from Lion trial, France, were based on 1024 patients treated by lumpectomy with negative margins and 50 Gy tangential radiation to the whole breast, randomised to either 10 Gy boost or no further RT. The relative risk for local recurrence at the 5th year was higher in the no-boost arm (4.5% compare to 3.6%) (p <0.044) and the authors advocate the benefit of boost irradiation in case of negative margins [17].

The EORTC boost trial increased the cohort and includes 5318 patients to prove or disprove the benefit from 16 Gy boost irradiation after lumpectomy with negative margins [18, 19]. The absolute benefit was 2.5% at the 5th years with a significant decrease of local recurrences from 6.8% in the no-boost arm compared to 4.3% in the boost arm (p<0.0001). In younger patients boost RT showed higher advantage for LTC than in the patients over 50 years of age. EORTC trial concludes that boost irradiation is essential in case of unclear or positive margins after lumpectomy.

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We could not investigate the relation between surgical margins and boost irradiation. A clear evidence of margins status could not be found in the operative protocols of all patients. In a number of them, the information was lacking, because evaluating procedure of surgical margins still is not a routine practice in some Bulgarian hospitals. In some cases, the precise information about volume of exised breast was also missing. So, the margin status of our patients could be addressed as unknown, as cited in many publications

Trying to overcome the disadvantage of the low numbers of events, we performed a regression analysis by proportional multivariate hazard Cox model. We analyzed the influence of several prognostic parameters (PP) on RFS in each group: tumour size 2.1-3 cm versus smaller size, degree of differentiation (G3 versus G1 plus G2), volume of axillary clearance (under and over seven negative lymph nodes) and tumour steroid receptors status (positive versus negative) (Table III).

PP as bigger tumour size (p=0.0125), G3 (0.0001), negative steroid receptors (0.0068) have a negative influence on RFS of non-boost arm.

The boost irradiation overcome the above registered negative influence of bigger pT, G3 and negative hormonal receptors on local RFS (Table III).

Proportional Cox regression analysis did not reveal influence of other parameters as negative prognostic

Table III. Influence of boost irradiation on Recurrence – Free Survival related to four tumour parameters. The analysis was performed by Proportional Hazard Cox model

Parameter	Chi²	df	p value
RFS in patients without boost irradiation	Chi² 55.5	df=4	p=0.00001
Variables	β		
Tumour size (2.1-3 cm)	-0.23		p= 0.01
Volume of axillary dissection	-0.02		p=0.06
Degree of differentiation (G)	-0.83		p=0.00
Positive steroid receptors	-0.15		p=0.006
RFS in patients with boost irradiation	Chi² 2.7	df=4	p=0.59
Variables	β		
Tumour size (2.1-3 cm)	-0.05		p=0.70
Volume of axillary dissection	-0.01		p=0.23
Degree of differentiation (G)	-0.21		p=0.29
Positive steroid receptors	-0.02		p=0.73

factors for local recurrence in both groups: microcalcifications, tumour necrosis, vessel invasion, tumour metaplasia, extensive intraductal component (EIDC), comedo structures

Our study does not pretend for final conclusive results. The figures of 3.4-3.6% local recurrence rate in both evaluated groups are among the lowest data cited in the literature. It might be a result of wider surgery with negative margins. Simultaneously, we achieved good cosmetic results in boost group that has been reported elsewhere [20].

The long term survival with equivalent evaluation of cosmetic results will reveal further information concerning ultimate local control rate as well as ultimate survival in relation to higher dose postoperative RT in BCS [21].

Conclusions

1. There was no significant difference registered in 10 years RFS (96%) in patients receiving 10 Gy boost irradiation, compared to 95% RFS of the patients irradiated by 50 Gy to the whole breast.
2. DFS was 89% at 10th year in the cohort of 341 patients after BCS in early breast cancer (pT<3 cm)
3. The relapse rate at 10th year was among the lowest figures reported – 3.4% for boost group and 3.6% for no-boost group.
4. Proportional hazard Cox model reveal a high-risk group for local recurrence that might benefited from boost irradiation after quadrantectomy with unknown surgical margin (tumour size 2.1-3 cm, G3, negative steroid receptors).

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