



BREAST CANCER ADJUVANT RADIOTHERAPY - WHEN CAN IT BE OMITTED?

KATARINA ANTUNAC¹ and LIDIJA BEKETIĆ-OREŠKOVIĆ^{1, 2}

¹Division of Oncology and Radiotherapy, University Hospital for Tumors,
Sestre milosrdnice University Hospital Center, Zagreb, Croatia;

²Department of Clinical Oncology, School of Medicine, University of Zagreb, Zagreb, Croatia

Summary

The aim of adjuvant radiotherapy in patients with breast cancer is to reduce the risk of disease recurrence; both local and systemic. It also contributes to better overall survival. However, that effect is not consistent across all subgroups of patients. Bearing in mind radiotherapy's side effects, it is crucial to define patients in which radiotherapy effect on the control of the disease is so low that it can be safely omitted. In general, those would be patients age 70 years or older after breast conserving surgery with hormonal receptor positive tumors, which are smaller than 2 cm (T1) and with uninvolved axillary lymph nodes (N0). It is a matter of discussion whether the same can be applied on HER2 + tumors, on tumors size up to 3 or even 4 cm, or in patients older than 65 or even older than 60 years. Upon mastectomy, radiation should be omitted in patients with tumors lesser than 5 cm and with uninvolved lymph nodes (pT1-2N0 stage). In case cancer treatment started with neoadjuvant systemic therapy, radiotherapy is always indicated after breast conserving surgery, but after mastectomy in clinically or pathohistologically positive lymph nodes (tumor stage cN+ or ypN+). Pathological response of the tumor on given systemic treatment should not be the major factor determining the decision about indication for radiotherapy.

KEYWORDS: *breast cancer; breast conserving surgery, mastectomy, adjuvant radiotherapy, radiotherapy after neoadjuvant systemic therapy*

INTRODUCTION

When setting up an indication for adjuvant radiotherapy, regardless advances in tumor biology cognition and possibilities of systemic treatment, the most important factor is local stage of the disease: size of primary tumor, number of positive axillary lymph nodes, number of evaluated axillary lymph nodes and type of the surgical procedure: breast conserving surgery (tumorectomy or quadrantectomy) or radical surgical procedure (mastectomy).

In 2011, meta analysis of 17 randomised clinical trials on adjuvant radiotherapy after quadran-

tectomy has been published, corroborating adjuvant radiotherapy in all patients with invasive breast cancer after quadrantectomy. Trials were undertaken between 1976 and 1999, all together 10 801 patients were included(1). Meta analysis supporting radiotherapy after mastectomy in all patients having at least one positive axillary lymph node was published in 2014 and it included 8135 patients from 22 randomised clinical trials that went on between 1964 and 1988(2).

Though it takes long follow-ups to show effect of radiotherapy on both local control and breast cancer survival, it is to notice that patients included in abovementioned meta analysis were diagnosed and treated differently than patients nowadays. Some diagnostic procedures were not available at the time, such as breast MRI, sentinel lymph node biopsy, detailed lymph node analysis

Corresponding author: Katarina Antunac, Division of Oncology and Radiotherapy, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Ilica 197, 10 000 Zagreb, Croatia. e-mail: katarina.antunac@gmail.com

such as immunohistochemical analysis or detection of isolated tumor cells within the lymph nodes. Not much was known about tumor biology, mostly data on tumor grade and hormonal receptor status are given and systemic antineoplastic treatment options were scarce; patients received either tamoxifen or obsolete chemotherapy protocols such as CMF.

Adjuvant radiotherapy's primary effect is on the local control of the disease. However, contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment. In the majority of patients more efficacious systemic therapy will decrease the risk of death due to distant metastases, after which optimised locoregional control will, relatively, contribute more to survival(3).

One should bear in mind radiotherapy's late toxicity, primary cardiotoxicity and development secondary tumors. After longer follow up, higher mortality of abovementioned causes has been observed in irradiated patients, compared to non-irradiated patients. That reduces radiotherapy's effect on the mortality of breast cancer patients. It is to notice that it applies on patients irradiated with older techniques, e.g. those using cobalt machines(4).

All of the above create the need to define subsets of patients in which adjuvant radiotherapy could be safely omitted. Those would be the patients whose risk of the disease recurrence is so low that it cannot be further reduced by radiotherapy. At the same time, radiotherapy in these patients could have negative effect on their quality of life.

Here we present literature data on the topic.

METHODS

Literature search with key words using PubMed was performed.

RESULTS

Omitting adjuvant radiotherapy in patients after breast conserving surgery

Adjuvant radiotherapy was always indicated in patients undergoing breast conserving surgery until 2004 CALGB 9343 trial has been published. Patients age 70 or older with pT1N0 HR positive

tumors were randomised to either radiotherapy plus 5 years of tamoxifen or tamoxifen only in period between 1994 and 1999. After 5 years of follow up, patients randomised to tamoxifen only had higher rate of local relapse (1% vs. 4%). No difference in rate of mastectomy due to relapse, distant relapse or overall survival has been observed between the treatment groups, overall survival being 87% for tamoxifen plus radiotherapy and 86% for tamoxifen only. Results of this trial presented a milestone in the treatment of patients who had breast conserving surgery defining subset of patients who do not need adjuvant radiotherapy as it does not contribute to the overall disease control(5).

In 2017 meta analysis including CALGB 9343 trial and three other randomised trials was published. Trials were conducted between 1989 and 2009 and included patients after tumorectomy receiving tamoxifen for 5 years. Patients were 65 or 70 years or older, median age was 70 years. Allowed tumors, size was up to 5 cm, but in majority of patients (83% - 99%) it was up to 2 cm. In less than 20% of patients tumors were grade III. In two trials estrogen receptors were positive in 97% and 99% of patients and in two other trials in 84% and 57% of patients. Patients were randomised to receive tamoxifen for 5 years, with or without adjuvant radiotherapy. After 5 years of follow up, on 1000 patients receiving tamoxifen only, 60 patients had local relapse, compared to 10 local relapses on 1000 patients undergoing adjuvant radiotherapy. This effect was consistent after 10 years of follow up. Relapse in axillary lymph nodes was also less common in irradiated patients: 3 on 1000 patients, compared to 12 on 1000 in tamoxifen only arm. No effect of adjuvant radiotherapy on distant relapse or overall survival has been observed(6).

PRIME II trial enrolled patients 65 years or older upon tumorectomy with ER and/or PR positive tumors size up to 3 cm and negative axillary lymph nodes. Patients received hormonal therapy, adjuvant +/- neoadjuvant and were randomised to receive adjuvant radiotherapy or not. After 10 years of follow up local relapse rate was statistically significantly higher in patients who were not irradiated; almost 11 times, exact figures being 9.8% in non-irradiated patients and 0.9% in irradiated patients. No difference regarding regional relapse, distant relapse, contralateral breast tumor or second primary malignancy has been

observed between the treatment groups. Overall survival was 80.4% in non-irradiated patients and 81% in irradiated patients. Just 11 out of 1326 patients died of breast cancer; 3 of them were irradiated. In patients who underwent adjuvant radiotherapy only 4% of all deaths were caused by breast cancer, compared to 9% of all deaths in patients receiving endocrine treatment only(7).

Most of these trials were conducted in the last decade of 20th century and early years of 21st century when HER2 was not routinely tested and adjuvant anti-HER2 therapy was not available. That leaves us with question whether it is safe to omit adjuvant radiotherapy in patients with HER2 positive tumors that otherwise fulfil criteria for radiotherapy omission. Retrospective analysis conducted by Bazan et al. included 6400 patients from National Cancer Database with pT1N0 HER2 positive tumors. Patients received adjuvant chemotherapy and anti-HER2 therapy. Part of the patients was 70 years or older and part of the patients had HR positive tumors. Multivariate analysis showed correlation between higher risk of death and omission of radiotherapy(8).

Though clear randomised trials data are lacking and patients old 70 years or more with pT1N0 ER positive HER2 positive tumors not receiving chemotherapy are substantially rare, when setting up indication for adjuvant radiotherapy in these patients great care should be applied and it should not be easily omitted.

Clinical trials examining safety of adjuvant radiotherapy omission in patients aged 50 years or more are ongoing, but tumor biology is taken into an account. These trials are mainly focusing on Luminal A breast cancer.

Since adjuvant endocrine therapy should be taken for at least 5 years and it, undoubtedly, has its side effects, having in mind patient's compliance, clinical trials comparing adjuvant radiotherapy only with endocrine therapy only are ongoing. So far we have retrospective data from National Cancer Database including 3000 patients aged 70 years or more with HR positive HER negative tumors staged pT1N0. 65% of patients received endocrine therapy only and 35% of patients were irradiated only, without endocrine treatment. After 4 years of follow up, no difference in overall survival between the treatment groups has been shown(9). Based on these data, it would be wise in some patients to conduct only adjuvant ir-

radiation during 3 weeks, rather than prescribe endocrine therapy for 5 years.

Omitting adjuvant radiotherapy after mastectomy

After mastectomy, adjuvant radiotherapy is omitted in patients with pT1-2N0 stage of the disease.

EBCTCG meta analysis published in 2014 demonstrated that adjuvant radiotherapy in patients with pT1-2N+ stage of the disease reduces the risk of disease relapse and death(2). Traditionally, the difference between pT1 and pT2 stage is based on number of lymph nodes that are involved with tumor: 1-3 positive lymph nodes being pN1 and 4 or more positive lymph nodes being pN2. In practice, patient's prognosis is not much different whether 3 or 4 lymph nodes are involved with tumor. Nevertheless, there is substantial difference between 1 small metastasis in one lymph node and bulky involvement of all 3 lymph nodes with extracapsular tumor spreading; yet both entities are classified as pN1 stage of the disease. Therefore, patients with pT1-2N1 stage of the disease present a heterogeneous group of patients and in some of them adjuvant radiotherapy could be safely omitted. That primarily applies on patients with advanced age, multiple comorbidities, short life expectancy, pT1 tumors, only one lymph node affected with tumor, small metastasis, low tumor grade, absence of lymphovascular invasion, HR positive and HER2 negative tumors. In these patients benefit of adjuvant radiotherapy on overall survival is probably so low that it does not justify its risks(10).

However, adjuvant radiotherapy can be considered in patients with pT2N0 stage of the disease whose tumors are size 4 cm or bigger or in presence of lymphovascular invasion.

In practice we rarely see patients whose primary therapy is radical mastectomy; in patients requiring mastectomy nowadays treatment usually starts with neoadjuvant systemic therapy.

Omitting adjuvant radiotherapy after neoadjuvant systemic therapy

Indication for adjuvant radiotherapy is based on initial local stage of the disease- prior to beginning of treatment. In patients whose primary treatment is surgical procedure, the decision for

adjuvant radiotherapy is based on detailed pathohistological finding, which is still superior to any modern diagnostic method. In patient whose treatment start with neoadjuvant systemic therapy, that initial pathohistological finding is missing. In these cases, decision on adjuvant radiotherapy is based on initial clinical stage of the disease. We must have detailed clinical examination, imaging evaluation and cytology or biopsy of suspected axillary lymph nodes. Another important data is type of surgical procedure; adjuvant radiotherapy is always indicated after tumorectomy.

Therefore, it is crucial to define group of patients in which mastectomy followed neoadjuvant systemic therapy that could be spared adjuvant radiotherapy. Those would be patients clinically presented as T1-2 N0 stage of the disease. That stage has to be confirmed by clinical examination, breast and axilla MRI and breast and axilla ultrasound with cytopunction or biopsy of any lymph node suspicious on malignancy. In case of at least one suspected lymph node by any of these methods, adjuvant radiotherapy is to be considered. Decision on adjuvant radiotherapy should never be based on definite pathohistological finding after surgical procedure; that finding just helps in the definition of target volumes.

Pathological complete response (pCR) is correlated with patient's prognosis but it does not mean the disease is cured; it simply means that the tumor responded to systemic therapy that was already given. In proportion of patients achieving pCR disease relapse will occur and in proportion of patients not achieving pCR there will be no disease relapse. Besides prognostic value, pathologic response rate serves as guidance for subsequent adjuvant systemic therapy.

Neoadjuvant systemic therapy in patients with resectable breast cancer is relatively new concept and it has been used routinely for less than a decade. It takes time for curative intervention such as adjuvant radiotherapy to demonstrate its effect on the disease control and overall survival. That time is measured in decades. Therefore, it is clear that, so far, we are lacking results of randomised clinical trials on adjuvant radiotherapy in patients undergoing neoadjuvant systemic therapy. What we do have and rely on when setting up an indication for adjuvant radiotherapy, is a number of retrospective analyses.

National Cancer Database analysis included the data of 15 000 patients with cT1-3N1-2 stage of the disease receiving neoadjuvant systemic therapy between 2003 and 2011. Patients were divided in 4 cohorts based on the type of surgical procedure: mastectomy or tumorectomy and based on post-chemotherapy pathological stage of lymph nodes: ypN0 or ypN+. Patients undergoing adjuvant radiotherapy after mastectomy had better overall survival, regardless of ypN stage of the disease, age, comorbidities, clinical T stage of the disease, pathological response rate, hormonal receptors status and type of surgical procedure in axilla: dissection or sentinel lymph node biopsy(11).

Montero et al. analysed the data from 11 clinical trials on breast cancer patients with clinically positive lymph nodes prior to neoadjuvant systemic therapy. If in patients with pathological complete response in lymph nodes (ypN0) adjuvant radiotherapy was administered, relapse rate was 3.15%. In case radiotherapy was omitted, relapse occurred in 24.4% of patients. In patients with residual disease in lymph nodes after neoadjuvant systemic therapy (ypN1), relapse rates were 10.8% with adjuvant radiotherapy and 56.25% without adjuvant radiotherapy. In conclusion, patients who achieved pCR had double risk of local relapse in absence of radiotherapy compared to patients that did not achieve pCR but underwent adjuvant radiotherapy.

According to these authors, omission of adjuvant radiotherapy in patients after neoadjuvant systemic therapy followed by mastectomy can be considered if patients were aged 40 years or more, had tumors in clinical stage II (except cT3N0), tumor type is luminal A, pCR was achieved in both breast and lymph nodes and in absence of lymphovascular invasion and extracapsular spreading(12).

Omitting adjuvant radiotherapy in patients with ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ accounts for about 20% of breast cancer. It is asymptomatic in most patients and it is diagnosed with screening mammography. Tumor is not invasive, but local relapse rate is up to 30%. Half of these relapses can be in form of invasive disease(13).

According to the results of EBCTCG meta analysis that included 4 randomised clinical trials

conducted between 1985 and 1999, adjuvant radiotherapy absolutely reduces 10- year risk of ipsilateral ductal carcinoma in situ for 15%; relapse rates were 12.9% in irradiated patients and 28.1% in non-irradiated patients. That risk reduction applies on both in situ and invasive relapse and is consistent regardless of patient's age, extensiveness of surgical procedure, tamoxifen use, resection margins, tumor focality, tumor grade, presence of comedo necrosis, tumor size and method of tumor diagnosis (whether the tumor was symptomatic or was diagnosed with screening mammography). Risk reduction has been observed even in small low grade tumors with clear resection margins. After 10 years of follow up, no effect of adjuvant radiotherapy on mortality, breast cancer mortality or other cause mortality was shown (14).

However, except recurrence in ipsilateral breast, in about 10% of patients DCIS occurs in contralateral breast. Since DCIS presents heterogeneous group of tumors, not all types of DCIS have the same recurrence risk. Therefore, in some patients adjuvant irradiation could be omitted(13).

Considering pathohistological report, low risk DCIS would be tumors with low or intermediate grade, size up to 25 mm with at least 10 mm resection margin. 5- year local relapse rate in patients with low risk DCIS taking tamoxifen is about 6%. However, after 10 years, local relapse rate in this group of patients is almost 15%, meaning that even in patients with low risk DCIS one should be very cautious when considering omission of adjuvant radiotherapy (15,16).

In NRG/RTOG 9804 trial effect of adjuvant radiotherapy has been explored in patients with low or intermediate grade DCIS size up to 35 mm with resection margin of at least 3 mm. Median tumor size was 5 mm. Patients that underwent adjuvant radiotherapy had significant reduction of recurrence risk; after 7 years of follow up local relapse rates were 0.9% with adjuvant radiotherapy and 6.7% in absence of adjuvant radiotherapy. After 12 years of follow up, local recurrence occurred in 2.8% of irradiated patients and in 11.4% of non-irradiated patients. Rate of invasive disease recurrence was lower in irradiated patients: 1.5%, compared with 5.8% in non-irradiated patients(17).

In conclusion, even in patients with low risk DCIS, adjuvant radiotherapy significantly reduces both local relapse rate and invasive disease recurrence rate.

According to the results of OncotypeDX DCIS gene expression analysis test showed as recurrence score (RS), patients can be stratified in three risk groups:

1. Low risk (RS < 39)- ipsilateral disease recurrence risk 12%
2. Intermediate risk (RS 39- 54)- ipsilateral disease recurrence risk 25%
3. High risk (RS > 54)- ipsilateral disease recurrence risk 27%

If patients underwent adjuvant radiotherapy, recurrence rates were 7.5% in low risk group, 13.6% in intermediate risk group and 20.5% in high risk group. In all risk groups adjuvant radiotherapy reduced the risk of the disease recurrence, even though absolute benefit was lower in low risk group. Prior to becoming standard part of clinical practice, test is being further validated(18).

Omission of adjuvant radiotherapy is probably reasonable option in patients with advanced age and comorbidities in case of low grade tumors. Although adjuvant radiotherapy did not show any effect on overall survival, it should not be omitted in large tumors, high grade tumors, tumors presenting as palpable mass, tumors with close or positive resection margins and in patients younger than 50 years(19).

CONCLUSION

It is inevitably proven that adjuvant radiotherapy reduces the risk of local relapse of breast cancer. Contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment. However, having in mind late toxicity of radiotherapy, its costs and inconvenience, it is crucial to cautiously define subsets of patients whose prognosis is so good that adjuvant radiotherapy cannot significantly contribute to the disease control and can be safely omitted.

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Sažetak

KADA SE MOŽE OTKLONITI INDIKACIJA ZA ADJUVANTNU RADIOTERAPIJU RAKA DOJKE?

K. Antunac, L. Beketić-Orešković

Adjuvantna radioterapija kod bolesnica s rakom dojke provodi se s ciljem smanjenja rizika povrata bolesti: lokalnog i sustavnog te je njome moguće postići i bolje ukupno preživljenje. Međutim, taj učinak radioterapije nije jednak u svim skupinama bolesnica. Kako zračenje ima i određene nuspojave, potrebno je definirati bolesnice kod kojih je učinak radioterapije na sveukupno kontrolu bolesti toliko malen da se ovaj oblik liječenja može i izostaviti. To su, načelno, bolesnice starije od 70 godina kod kojih je učinjen poštedni kirurški zahvat a tumori imaju pozitivne hormonske receptore, manji su od 2 cm (T1) i aksilarni limfni čvorovi nisu zahvaćeni (N0). Uпитno je može li se indikacija za radioterapiju u toj skupini bolesnica otkloniti i u slučaju Her2 pozitivnih tumora, tumora veličine do 3 ili 4 cm te kod bolesnica starijih od 65 ili čak 60 godina. U slučaju provedenog radikalnog kirurškog zahvata radioterapija se izostavlja kod tumora manjih od 5 cm i nezahvaćenih limfnih čvorova aksile (pT1-2, N0). Ukoliko je provedeno neoadjuvantno sustavno liječenje, radioterapija se provodi uvijek nakon poštednog kirurškog zahvata, a nakon radikalnog kirurškog zahvata uvijek kod klinički ili patohistološki pozitivnih limfnih čvorova aksile (cN+ ili ypN+). Kriterij otklanjanja indikacija za radioterapiju nikako ne bi smjela biti isključivo stopa patološkog odgovora na provedenu neoadjuvantnu sustavnu terapiju.

KLJUČNE RIJEČI: *rak dojke; poštedni kirurški zahvat; radikalni kirurški zahvat; adjuvantna radioterapija; radioterapija nakon neoadjuvantne sustavne terapije*