REVIEW

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Deescalation of axillary radiotherapy – is now the time to start?

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Summary

Indication for radiotherapy of regional lymph nodes in patients with breast cancer is based on the clinical stage of the disease, surgical procedure, intraoperative and pathohistological report. It is supported by a meta-analysis of randomized clinical trials with long follow-up. However, many of these trials were performed decades ago, and, in the meantime, tremendous progress has been made in diagnostics, understanding of tumor biology, tailoring and effectiveness of systemic treatment, and technical possibilities of radiotherapy. Based on these new data, the approach to the axillary radiotherapy should be tailored, and a subset of patients in which de-escalation of axillary treatment is feasible defined.

KEYWORDS: *breast cancer, adjuvant radiotherapy, axillary lymph node dissection, sentinel lymph node biopsy, radiotherapy after primary systemic therapy, axillary radiotherapy*

INTRODUCTION

In accordance with existing guidelines, the indication for adjuvant radiotherapy in patients with breast cancer initially treated with surgery is based on the intraoperative findings, the extent of the surgical intervention, and the pathohistological findings. Therefore, radiation of the regional lymphatic drainage is always indicated if more than more than pathologic 3 lymph nodes were found, and most often even if one lymph node is affected by the tumor(1). If only a biopsy of the sentinel lymph node was performed, all levels of the axilla are irradiated if at least 1 lymph node is affected by the tumor(2). In principle, the dissected part of the axilla is not irradiated, except in cases of suspected residual disease (e.g., less than 6 lymph nodes were examined, more than half of the examined lymph nodes were affected by tumor, if there was a presence of extracapsular extension, or if there was residual macroscopic disease in the axilla). Radiation is not indicated in the case of micrometastasis in the lymph node. The above is well supported by the results of randomized clinical trials and meta-analyses(3).

In cases where treatment has started with primary systemic therapy, the indication for radiotherapy is based on the initial clinical stage of the disease, the extent of the surgical procedure, and the histopathological findings. In principle, radiotherapy is always performed if at least one lymph node was initially affected by the tumor, regardless of the final histopathological findings and the response of the tumor in the lymph nodes to the primary systemic therapy. In the absence of results from randomized clinical trials, the indication for radiotherapy is defined on the basis of retrospective analyses(4,5).

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However, radiotherapy of lymphatic drainage can result in significant toxicity. According to the results of the EORTC study, which included over 4000 patients with breast cancer who received adjuvant radiation with standard fractionation between 1996 and 2004, after 15 years of follow-up, a higher incidence of pulmonary fibrosis (5.7%), cardiac fibrosis (1.9%), and any heart disease (11.1%) was found. This increased toxicity was found in patients whose target volumes included nodes along the internal mammary artery and supraclavicular lymph nodes, compared with patients who did not receive lymphatic drainage radiation, regardless of the side of the body that was irradiated. There was no difference in the occurrence of a second primary tumor, a tumor in the contralateral breast, or death from a cardiovascular event. There was no difference in the overall survival; however, patients who received lymphatic drainage radiation had a lower risk of disease recurrence and a lower risk of death from breast cancer(6).

Based on the constant arrival of new results from clinical studies and with the aim of individualizing the treatment of patients with breast cancer, it is necessary to define when and in which groups of patients we can de-escalate lymphatic drainage radiotherapy without compromising the outcome of the treatment.

The results of recent clinical studies and the consensus from 2023 will be presented below.

AXILLARY RADIOTHERAPY IN PATIENTS WHOSE TREATMENT BEGINS WITH SURGERY

A study by Whelan et al., published in 2015, included 1,832 patients who underwent breast segmentectomy and axillary dissection between 2000 and 2007 and who either had positive axillary lymph nodes or had negative nodes but were at increased risk of disease recurrence. These included tumors larger than 5 cm, tumors 2–5 cm in size with fewer than 10 lymph nodes examined, grade 3 tumors, ER-negative tumors, and tumors with lymphovascular invasion. Patients were randomized to receive breast radiation alone or to receive breast radiation plus regional lymphatic drainage: supraclavicular and infraclavicular lymph nodes and lymph nodes along the internal mammary artery. In patients with more than 3 positive lymph nodes or fewer than 10 lymph nodes examined, the target volume included the 1st and 2nd levels of the axilla. After a median follow-up of 9.5 years, there was no difference in the overall survival between groups. Patients who received radiation had longer disease-free survival and fewer regional recurrences, but at the cost of greater treatment toxicity.

Early side effects included radiation dermatitis and pneumonitis, while late side effects included lymphedema, and skin and connective tissue changes. Although this is one of the first studies to question the validity of lymphatic drainage radiation in patients with positive axillary lymph nodes, it is worth noting that it began more than 20 years ago. According to the guidelines at the time, treatment in all patients began with surgery, which would not be the case today, and the HER2 status of the tumor was not known, which greatly changes the approach to treatment and the prognosis of the patients. The patients were also irradiated with standard fractionation, which was later shown to be inferior to hypofractionated radiation(7).

The EBCTCG meta-analysis, which was published in 2018, included data from more than 13,000 patients from 14 randomized trials conducted up to 2009. In the studies conducted between 1961 and 1978, the median cardiac dose was estimated to be greater than 8 Gy, while the lymphatic drainage target volume coverage did not exceed 85%. In these patients, radiation had no effect on disease control or mortality from breast cancer, but the risk of death from other causes was found to be increased. Thus, the group of patients who received radiation for lymphatic drainage had a higher overall mortality compared to the group of patients who did not receive radiation of lymphatic drainage. On the other hand, in the studies conducted between 1989 and 2003, in which the median cardiac dose was less than 8 Gy and the lymphatic drainage target volume coverage was greater than 85%, radiation for lymphatic drainage reduced the risk of disease recurrence, death from breast cancer and total mortality without increasing the risk of death from other causes(8).

DE-ESCALATION OF AXILLARY RADIOTHERAPY AFTER NEOADJUVANT SYSTEMIC TREATMENT

In a 2021 publication in Cancer Treatment Reviews, a group of authors presented the results of previously published clinical studies and database analyses to answer the question of whether it is time to de-escalate the axillary approach(9). It is worth noting that, in regard to radiotherapy, these are mostly retrospective analyses(4,10,11,12). The biggest challenge is the issue of lymphatic drainage radiation after primary systemic treatment. It is clear that in patients who had a clinically negative axilla and who remained histologically negative after neoadjuvant systemic therapy and surgery, lymphatic drainage radiation is not necessary, while in patients with residual disease in the axilla, lymphatic drainage radiation is necessary. However, in patients who initially had positive lymph nodes and achieved a complete pathological response, the situation is less clear, especially if only a sentinel lymph node biopsy was performed, and not axillary dissection. These patients account for about 40% of all patients treated with neoadjuvant systemic therapy. The results are ambiguous; in principle, there is a lower risk of local recurrence, with or without impact on overall survival.

Data from the National Cancer Database analyses are presented in Table 1.

The authors recommend that consideration be given to removing the indication for axillary radiotherapy in patients with ypN0 stage disease who initially had a lower N stage, in older patients if breast irradiation is to be performed following segmentectomy, and in patients with aggressive tumor phenotypes who have achieved a complete pathological response. It is clearly recommended to irradiate only the part of the axilla that has not been resected, since recurrences occur in the unresected part of the axilla, and irradiating all levels of the axilla after dissection significantly increases the risk of lymphedema(9,13).

The prospective study published in 2022 included 838 patients with breast cancer of clinical stage cT2N1 (clinically 1-3 positive lymph nodes with at least one histologically confirmed) who underwent radiotherapy from 2011 to 2015. The patients received neoadjuvant systemic therapy and then underwent surgery. Considering the stage of the disease in the axilla, they were divided into 3 groups. Patients with stage ypN0 were considered a low-risk group. In this group of patients, only the breast was irradiated following segmentectomy, while radiation was omitted in patients who underwent mastectomy. Patients with stage ypN1 were considered an intermediate-risk group, and they received irradiation of the breast or chest wall without irradiation of the lymphatic drainage. Patients with stage ypN2 represented a high-risk group, and they received irradiation of both the breast/chest wall and lymphatic drainage. After 5 years of follow-up, locoregional recurrence rates were 2.1% for the low-risk group, 2.2% for the intermediate-risk group, and 2.3% for the high-risk group, so there was no difference between the groups in terms of local disease control(14).

What after primary hormonal therapy?

More and more patients with hormone-positive tumors are receiving neaodjuvant endocrine therapy before surgery. Pathological complete response occurs in less than 10% of patients (for comparison, the pathological complete response rate to chemotherapy is about 15%). Since it is unlikely that a few weeks of endocrine therapy will

Table 1.

Effect of lymphatic drainage radiotherapy in cN1 ypN0 disease stage, data from National Cancer Database analyses(9)

Author, period (ref)	Type of surgical procedure	No of patients	Overall survival (OS)
Rusthoven, 2003.-2011. (4)	mastectomy	3040	Improved OS
Liu, 1998.-2009. (10)	mastectomy	1560	Better OS in stage IIIB/IIIC, T3/4 and without pCR in the breast
Fayanju, 2010.-2015. (11)	mastectomy	7499	No OS benefit
Kantor, 2004.– 2008. (12)	mastectomy	1937	Better OS only in ER – tumors
Rusthoven, 2003.-2011. (4)	segmentectomy	2070	No OS benefit
Fayanju, 2010.-2015. (11)	segmentectomy	4842	No OS benefit

Table 2.

Summary of recommendations for radiotherapy of the axilla, Lucerne Toolbox 2 (14)

Tumor stage	Consensus	Discussion
cT1, cN0	In medially and centrally located tumors, nodes along the internal mammary artery and the 3rd-4th level should not be included in the target volume.	For high-risk tumors, include the mentioned regions in the target volume
cT1, cN0, SLNB not performed	None	Perform breast irradiation with tangential fields; the lower part of the axilla will receive radiation.
cT1-2, cN1, treatment began with surgery, pN1	For low-risk tumors, perform irradiation of the 1st and 2nd levels of the axilla and interpectoral nodes. For higher-risk tumors, consider irradiation of all levels of the axilla (1-4). For medially and centrally located tumors, nodes adjacent to the internal mammary artery should be included in the target volume.	Recommendations based on ACOSOGZ0011 and AMAROS trial.
cN1, PST	cN1, ypN0 In low-risk tumors, if axillary dissection or SLNB has been performed, radiation should be given to the 1st and 2nd levels of the axilla and interpectoral nodes. In higher-risk tumors, radiation should be given to all levels of the axilla (1-4). In medially and centrally located tumors, nodes adjacent to the internal mammary artery should be included in the target volume.	Review pre-PST images, fusion with pre-therapy PET CT. Limited ability in histological assessment of complete pathological response. Do not de-escalate all therapeutic options.
	pN1, ypN1 If axillary dissection has not been performed, perform irradiation of all levels of the axilla. For medially and centrally located tumors, nodes adjacent to the internal mammary artery should be included in the target volume.	Perform a biopsy of l. nodes suspicious on simulation CT, if they are not resectable, give a “boost” dose.
cN2-3, PST	cN2-3 after dissection: include only the undissected part of the axilla, regardless of response to therapy.	Include the dissected portion of the axilla in the target volume if residual disease is suspected. Limited data on the efficacy of boost doses in unresectable disease. Low risk of toxicity, goal is to achieve better local control.
	ypN0 Add “boost” to unresectable lymph nodes suspicious on post-PST scans.	
	ypN+ Add “boost” to initially highly suspicious or involved lymph nodes (proven by biopsy) that have not been resected.	

lead to the conversion of cN1 stage disease to ypN0, this group of patients should be considered as if they had initially undergone surgery, and the pathohistological findings should be interpreted as a guide for setting the indication for radiation(9).

The Lucerne Toolbox- 2nd consensus is a multidisciplinary consortium of European Oncology Societies and representatives of patient associations that focuses on the challenges in the management of the axilla in patients with breast cancer – from diagnosis to local therapy(15).

The recommendations regarding radiotherapy to the axilla:

1. Radiotherapy should be standardized, with indications and definition of the target volume in accordance with ESTRO recommendations and the risk of lymph node involvement. It is necessary to fully clarify the surgical procedure performed in the axilla.

2. Any lymph node suspicious on simulation CT should be biopsied before the start of radiation.

3. In patients with cN3 stage of disease, following neoadjuvant systemic therapy and axillary dissection, a *boost* dose should be given to any initially highly suspicious or biopsy-proven positive lymph node if there is residual disease, regardless of radiological response.

4. All patients with stage cT1-2 pN1 disease (3 or fewer suspect lymph nodes) who have not undergone axillary dissection should receive radiation to all levels of the axilla, regardless of risk factors. For medially or centrally located tumors, the target volume should also include nodes adjacent to the internal mammary artery.

Recommendations for lymphatic drainage radiotherapy, depending on the stage of the disease and the treatment performed, are presented in Table 2.

CONCLUSION

In patients with breast cancer, the decision on the need for axillary radiotherapy should be individualized, taking into account the risk of disease recurrence, reduction of radiation side effects, and efficacy. Most data indicating a possible de-escalation of axillary radiotherapy are actually retrospective analyses, and in the absence of results from prospective randomized clinical trials, the removal of the indication for radiotherapy should be approached gradually and with great caution.

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Sažetak

Deeskalacija aksilarne radioterapije – je li došlo vrijeme?

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Indikacija za radioterapiju limfne drenaže kod bolesnica s rakom dojke donosi se temeljem inicijalnog kliničkog stadija bolesti, vrste kirurškog zahvata, intraoperativnog nalaza te patohistološkog nalaza, a bazira se na rezultatima meta analiza randomiziranih kliničkih studija s dugim praćenjem bolesnica. Međutim, navedene studije su provedene prije više desetljeća, a u međuvremenu su postignuti znatni napreci u dijagnostici tumora, poznavanju biologije bolesti, individualizaciji i učinkovitosti sustavnog antineoplastičnog liječenja te tehničkim mogućnostima radioterapije. U svjetlu navedenog, a na osnovu novih rezultata, nastoji se individualizirati pristup adjuvantnom zračenju limfne drenaže te definirati skupine bolesnica kod kojih se može provesti deeskalacija radioterapije.

KLJUČNE RIJEČI: *rak dojke, adjuvantna radioterapija, disekcija aksile, biopsija limfnog čvora stražara, radioterapija nakon primarne sustavne terapije, radioterapija aksile.*