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COMMENTARY

Axillary irradiation omitting axillary dissection in breast cancer: is there a role for shoulder-sparing proton therapy?

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ABSTRACT

The recent EORTC 10981-22023 AMAROS trial showed that axillary radiotherapy and axillary lymph node dissection provide comparable local control and reduced lymphoedema in the irradiated group. However, no significant differences between the two groups in range of motion and quality of life were reported. It has been acknowledged that axillary irradiation could have induced some toxicity, particularly shoulder function impairment. In fact, conventional breast irradiation by tangential beams has to be modified to achieve full-dose coverage of the axillary nodes, including in the treatment field a larger portion of the shoulder structures. In this scenario, alternative irradiation techniques were discussed. Compared with modern photon techniques, axillary irradiation by proton therapy has the potential for sparing the shoulder without detrimental increase of the medium-to-low doses to the other normal tissues.

After the advent of conservative breast cancer therapy, morbidity of combined surgery and radiotherapy (RT) still remains a matter of debate. Since a substantial proportion of patients report moderate or marked arm and shoulder symptoms, axillary lymph node dissection (ALND) may be omitted in specific groups of patients. At least some of these patients would likely profit from regional RT.¹

In the recent EORTC 10981-22023 AMAROS trial, ALND was compared with axillary radiotherapy (AxRT) in node-positive patients.² The results of the trial confirmed that both AxRT and ALND provide comparable local control and showed reduced lymphoedema in the AxRT group. However, no significant differences were observed between the two groups regarding range of motion (ROM) and quality of life. These findings raised some discussion on the potential effect of the additional irradiation produced to the shoulder's structures by AxRT, as it was hypothesized that the dose delivered in the AxRT group counteracted the benefits expected by omitting ALND.³

The magnitude of the late effects of treatment for breast cancer on shoulder function 1 year or more after diagnosis, with a focus on RT, was reviewed by Levangie and Drouin.⁴ They reviewed 10 studies (total number of patients: 1520) comparing RT with no RT or RT in a different area.

Two of five studies that compared RT with no RT reported no evidence of between-group differences; the other three reported statistically significantly increased odds for various outcomes that included flexion and abduction ROM, pain and loss of mobility. All five studies that compared chest/axillary RT with chest only or no RT reported statistically significant limitations for chest/axillary treatment for outcomes that included abduction or flexion ROM, internal and external rotation and impaired mobility. Regarding RT to the axilla and chest *vs* RT to the chest, a relative risk of 1.7 was observed in one included study and reduced ROM in 20–49% *vs* 4–14% of the study population in the other included studies.

In a successive review,⁵ comparing AxRT *vs* no AxRT, risk factors for reduced ROM in abduction, flexion and external rotation was reported at Level 1 evidence (using the Oxford Centre for Evidence-Based Medicine, 2011).

The shoulder morbidity induced by AxRT is likely related to the adopted irradiation technique, as shown in Figure 1. Conventional whole-breast irradiation is performed by standard tangential fields (Figure 1a), which typically include only part of the axilla⁶ and the shoulder.⁷ Irradiation of the Level I and II axillary lymph node volumes requires significant modification of standard tangential fields to achieve adequate dose coverage in the axillary region.⁶ As

Figure 1. Dose distributions in axillary radiotherapy (AxRT) techniques. (a) Conventional whole-breast irradiation by tangential irradiation without full axillary coverage. (b) AxRT by modified tangential beams. (c) Shoulder-sparing AxRT by non-tangential intensity-modulated irradiation. (d) Shoulder-sparing AxRT by proton therapy. Planning target volumes of the breast (PTVb) and of the Level I-II lymph nodes (PTVn) are shown. The involved shoulder structures are indicated by black arrowheads (a–d). The reported isodoses are 95%, 60% and 40% of the prescribed dose (50 Gy).

a consequence of full nodal AxRT, in some patients, a large portion of shoulder structures is included in the treatment fields (Figure 1b).

In the literature, the organ that needs to be spared to limit potential shoulder morbidity has not yet been fully clarified. In a cohort of 183 patients, significant correlations were found between shoulder joint volume receiving a dose of approximately 15 Gy and clinical end points such as arm pain, arm stiffness, swollen arm, use of arm, numbness and impaired shoulder abduction.⁸ Stubblefield, in his review,⁹ reported that any structure with tendons or neurovascular innervation traversing the field can be affected by radiation fibrosis syndrome. Neuromuscular and musculoskeletal complications can be observed even in patients typically treated by 30–36 Gy, as reported in long-term Hodgkin's lymphoma survivors.⁹ Higher doses might increase the risk of myositis and muscle fibrosis. In the newly published ESTRO consensus for target delineation in breast cancer,¹⁰ it has been recommended to avoid inclusion in the clinical target of the scapulohumeral joint and the connective tissues around this joint.

Because the AMAROS protocol was written and initiated in the late 1990s, it has been acknowledged that AxRT could have induced some toxicity in the AMAROS trial, particularly shoulder function impairment and that irradiation of the shoulder muscles can be diminished with modern irradiation techniques of the axilla.¹¹

In this scenario, alternative irradiation techniques have to be discussed. Non-tangential and rotational techniques can decrease the dose to the shoulder, but at the expense of an increase of the lower doses to the other normal tissues, which might be detrimental when extensively adopted in long-term surviving patients.¹² In fact, even after conventional radiation treatment, long-term outcomes have raised concerns about increased risk of cardiac and pulmonary toxicity and increased incidence of contralateral breast cancer and other secondary malignancies. In Figure 1c, the dose distribution is obtained by non-tangential intensity-modulated radiation therapy as a compromise between shoulder sparing and normal tissues sparing. Further decreasing the medium-to-low dose to the shoulder might reduce morbidity but would

increase the volume of the other normal tissues receiving the same dose.

Proton therapy (PT) has the potential for sparing the shoulder in axillary irradiation (Figure 1d) without increasing the dose to other normal tissues, as proton dose deposition occurs in a defined range. The dosimetric advantage of proton radiation for the treatment of breast cancer has been demonstrated when attempting to cover regional lymph nodes,¹³ and initial clinical studies reported that PT was feasible and well tolerated.¹⁴ Furthermore, the treatment by pencil beam scanning¹⁵ markedly limits undesired neutron production, which might be highly effective in inducing second cancers.

Despite substantial capital and operational costs, several proton facilities have recently opened or are in planning or construction phases. Moreover, breast PT could be delivered with limited gantry angles and limited energies/ranges, so that dedicated cheaper systems (or treatment rooms) could be developed in the future. Since breast PT will become more and more available, it could be an effective therapeutic option in axillary irradiation.

In conclusion, we expect that PT can diminish the incidence of shoulder toxicity in the emerging therapeutic approach that replaces ALND with AxRT, and therefore, its evaluation should be the goal of a prospective study.

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