Potential risks and benefits of radiation therapy as adjuvant treatment in patients with low-risk carcinoma of the mammary gland: taking cutaneous postradiation angiosarcoma as an opportunity for a critical appraisal of postoperative radiotherapy

In this issue of *Annals of Oncology*, M. Moe and G. Bertelli [1] propose, in a ‘Letter to the Editor’, a number of interesting considerations on the clinical pattern and treatment of breast angiosarcoma, with emphasis on a woman presenting this disease after breast-conserving surgery (BCS) and radiotherapy, with a short latent period following her first-line treatment.

Their letter first calls for a number of comments on a typical example of radio-induced late effects, the occurrence of which always represents a source of profound frustration both for the patient and her radiation oncologist.

As an aggressive tumor of endothelial origin, angiosarcoma of the breast (AS) is occurring as idiopathic, lymphedema-associated, postirradiation, soft tissue, and various other clinical settings [1, 2]. Among these settings, iatrogenic AS, also known as ‘Stewart–Treves syndrome’ is usually attributed to chronic lymphedema, which can occur in a number of patients treated with BCS. Later on, with emphasis on breast-conserving therapy combined with adjuvant radiation, a form of cutaneous postradiation angiosarcoma of the breast (CPRASB) emerged from histopathologic reviews [3]. Characterized by a lack of association with lymphedema, CPRASB is frequently multifocal at presentation, most tumors have a vasoformative, sieve-like pattern of growth, and high-grade nuclear features.

Can we quantify the risk to develop a secondary angiosarcoma, following conventional, postoperative radiation doses? In 2001, a retrospective study conducted by Huang and Mackillop [4] on 194 798 breast cancer patients treated between 1973 and 1995, provides useful clues regarding this relative risk; in this cohort of patients, the age standardized incidence ratios for AS was 26.2 and 2.1 in the radiotherapy (RT) and non-RT cohort, respectively. Two other studies, published in 2005 and 2006, indicate that breast AS has a prevalence ranging between 0.002% and 0.005% per year [5], while the estimated overall incidence of breast angiosarcoma after breast-conserving therapy is low (0.14%), most of AS developing in cutaneous areas [6].

Actually is the prevalence of secondary AS higher than that of angiosarcomas in radiotherapy-naïve breasts in all retrospective studies? It does not seem to be the case. From a survey conducted in 11 French Cancer Centers [7], an AS prevalence of five cases per 10 000 was observed among 18 115 patients a majority of whom were T1N0M0 and node negative, which is the same prevalence for primary breast angiosarcomas occurring in healthy breasts.

Irradiated patients present with small, reddish, intradermal nodules over the treated area, which can also reveal hyperpigmentation, retraction, or discolored skin thickening. In some cases the clinical aspect can be mimicked by postirradiation morphea [8]; in case of AS the histologic pattern shows malignant cells with an endothelial immunophenotype in the cell block [9].

CPRASB is more often found in breasts developing postoperative and postirradiation edema and fibrosis [2]. It mainly affects women >60 and prevails in those who underwent axillary lymphadenectomy. Analyzing one of the largest cohorts of patients with AS, Vorburger SA et al. [10] also showed that the cases who had received prior radiation therapy were on average 30 years older than those presenting with radiation-naïve angiosarcoma.

Latent periods between the treatment of the breast cancer and the diagnosis of AS markedly vary across the retrospective studies, ranging from 5 to 26 years [5, 11, 12] with an average 14 years according to Kirova et al. [12]. Interestingly enough, secondary angiosarcomas can appear in the breast much earlier, e.g. as soon as a few months after lymphectomy and postoperative radiotherapy, as recently reported by Deutsch and Safyan [13] and by Moe and Bertelli, in this issue [1].

Traditionally, secondary AS is treated with mastectomy, and in some cases with postoperative chemotherapy. This disease has a dismal prognosis, especially in the presence of multiple skin lesions. Median survival rates are usually low, ranging from 12 to 33.5 months [11, 12]. Likewise, from a review by Rao et al. [14], the estimated 3-year overall survival for 58 patients was only 20%. The causes of failure are both local and systemic; reviewing the treatment outcome in 100 cases, Monroe et al. [15] showed that surgical excision is associated with very high rates of disease recurrence (55/75 patients, 73%). Distant metastases were also shown to develop simultaneously or shortly after local recurrences (LRs). In the French study mentioned above, Marchal et al. [7] report a median survival of 15.5 months. Interestingly enough, in the study by Vorburger et al. [10] mentioned above, the Kaplan–Meier curves were not statistically different between patients with radiation therapy-associated disease and radiation therapy-naïve patients.

Despite the fact AS developing in the wake of a radiation therapy are found quite infrequently, their occurrence in the follow-up of breast irradiation is an issue which should not be
radiation therapy and/or tamoxifen in women with tumors. From this randomized trial evaluating with margins of 1.0 cm or more. radiotherapy, a substantial risk of LR occurred after BCS alone cohort, there exist, in the absence of postoperative follow-up. This indicates that, even in a highly selected population of low-risk patients, in whom the second malignancy is really linked to postoperative irradiation; secondly, though not negligible, the incidence of the second malignancies developed in the wake of radiotherapy, remains an infrequent event. In this context, the contribution by Moe and Bertelli [1] also leads to address a second issue: are these risks of second malignancies counterbalanced by the therapeutic gain, in terms of enhanced local control, obtained by adjuvant radiotherapy in patients with (very) low-risk breast cancer? As a matter of fact, in the literature, there are few clues on the benefit patients presenting with small, low-grade breast carcinoma, for most reports on radiotherapy of minimal disease do not stratify their outcome analyses according to the histological grades or histological types. Can we nevertheless assess the potential risk of in-breast failure in a selected population of low-risk patients, in whom no adjuvant radiotherapy has been delivered? In a prospective study conducted, from 1986 to 1992, at Harvard Medical School, patients were required to have a unicentric, T1, pathologic node-negative invasive ductal, mucinous, or tubular carcinoma without an extensive intraductal component or lymphatic vessel invasion [18]. Surgery included local excision with margins of at least 1 cm or a negative reexcision. No RT or systemic therapy was given. At a median follow-up of 86 months, 19 out of 81 patients (23%) developed LR as a first site of failure, with average annual LR of 3.5 per 100 patient-years of follow-up. This indicates that, even in a highly selected cohort, there exist, in the absence of postoperative radiotherapy, a substantial risk of LR occurred after BCS alone with margins of 1.0 cm or more. These results actually confirmed the data provided by the NSABP-B21 study [19]. From this randomized trial evaluating radiation therapy and/or tamoxifen in women with tumors ≤1 cm, evidence had indeed been presented, that, in postoperative setting, radiotherapy was superior to tamoxifen (9.3 versus 16.5% of patients with local failure at a 8-year follow-up). The therapeutic gain observed for patients receiving radiotherapy was even enhanced when tamoxifen was combined to irradiation, with a 2.8% failure rate only in this latter group of patients. But how about radiotherapy outcome in the elderly presenting with low-risk breast carcinoma? In a large-scale study jointly conducted by the Cancer and Leukemia Group B (CALGB), Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Oncology Group [20], 636 women who were 70 years of age or older and who had clinical stage I (T1N0M0 according to the tumor–node–metastasis classification), estrogen receptor-positive breast carcinoma were randomly assigned to receive postoperatively tamoxifen plus radiation therapy (n = 317 women) or tamoxifen alone (n = 319). The only significant difference between the two groups was found in the rate of LR or regional recurrence at 5 years (1% in the group given tamoxifen plus irradiation and 4% in patients given tamoxifen alone, P < 0.001). There were no significant differences between the two groups with regard to 5-year rates of overall survival. The authors concluded that lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women 70 years of age or older who have early, estrogen receptor-positive breast cancer. In summary, while the effectiveness of radiation therapy in reducing LR after BCS in unsel ected patients with early-stage invasive breast cancer has been repeatedly substantiated, the ratio between benefits and risks of adjuvant radiotherapy in highly selected, low-risk breast cancer patients still remains to explore prospectively at a large scale. We should nevertheless keep in mind that, in terms of both late complications (here, essentially as regards second malignancies) and efficacy, these results derive from studies based on the principle of whole-bread irradiation with, in a significant number of cases, a rather large irradiation volume to the operated mammary gland and surrounding tissues. Are alternative approaches, using different techniques of irradiation, likely to alter the risks of late complications such as iatrogenic malignancies after BCS? As a matter of fact, a window of opportunity is currently under intensive investigation with respect to possible alterations brought to irradiated volume. Locally, breast cancer looks indeed like a segmental disease in the vast majority of patients with early disease and it has been repeatedly substantiated that most in-breast failures occur in the index quadrant [21]. In this context, strategies based on partial breast irradiation (PBI) are justified on a number of observations made in low-risk patients treated with conservative breast surgery. So far, with efficacy results at least as good as those observed after whole-bread irradiation, partial breast irradiation turns out to be associated with minimal long-term toxic effects [21]. Though still preliminary, the data released, in a recent past, on accelerated partial breast irradiation using intraoperative radiotherapy, the Mammosite device, interstitial brachytherapy, or external conformal radiotherapy, suggest novel treatment policies can be reasonably expected, at midterm, for low-risk disease management. Obviously, a number of questions still remain not fully answered. The clues gathered from preliminary
reports on feasibility studies suggest, we should prioritize investigations on the following issues: can we limit breast irradiation to tumor bed in patients presenting with small, unifocal disease, and at low risk of multicentric diffusion? Has patient’s age an impact on treatment outcome after partial breast irradiation? How can tumor grade and histotype (lobular invasive carcinoma, presence of in situ components, …) influence patient selection? Those are the main questions to be addressed prospectively, especially as regards low-risk breast cancer patients.

This also means that, until PBI safety and efficacy indices are not consolidated, these approaches are still investigational, even in patients with very low-risk prognosticators. In this perspective, the NASBP B39/RTOG 0413 trial, which compares, in stages 0–II breast cancer patients, whole-breast irradiation to partial breast irradiation is bound to provide a significant contribution regarding the impact of PBI on treatment outcome. Should prospective, randomized studies like this latter one clearly validate the relevance of partial breast irradiation in low-risk breast cancer patients, this latter modality would substantially modify the treatment algorithms in this breast cancer patient subpopulation.

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