Review Article

Radiation therapy for the elderly—change of concepts in breast cancer?

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Contributions: (I) Conception and design: A Szigeti, A Grajda; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: A Szigeti, E Szigeti; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The incidence of breast cancer in elderly patients has increased in the last years, perhaps due to better and earlier diagnostics and a longer life expectancy. Radiotherapy as a local adjuvant treatment after breast surgery, improves local control and overall survival. Due to frailty or comorbidity current guidelines cannot always be applied and the treatment decision-making process involving these older patients often remains the task of the treating physician rather than a fully established tumor board. The goal of this review is to summarize in short, the radiation therapy techniques available, and to outline the most important factors that could be relevant in the decision making for radiotherapy for elderly woman affected by invasive breast cancer.

Keywords: Breast cancer; radiation therapy; elderly

Submitted Jun 10, 2019. Accepted for publication Jun 26, 2019.
doi: 10.21037/tcr.2019.06.48
View this article at: http://dx.doi.org/10.21037/tcr.2019.06.48

Introduction

Increasing aging in cancer patients is a relevant and important issue and problem in the decision-making process in oncology. A rising number of patients with malignant disease is expected including breast cancer which stays as the most common cancer in women worldwide with over 2 million new cases in 2018 (1). With the continuous improvement of diagnostic methods and the widespread implementation of more efficacious screening processes most breast cancers can be detected much earlier than in previous decades. However, so far most current guidelines make no difference in the therapy strategy for women of advance age beyond 70–80 years or even older. Generally, the decision-making process involving older patients is complicated and remains often as a task for the physician rather than a fully established tumor board. The goal of this review is to outline the most important factors that could be relevant in the decision making for radiotherapy for elderly woman affected by invasive breast cancer.

Definition of elderly

What are the criteria for the elderly patient? WHO defines advanced age as 65 year or older, although 70 years are often considered as the "critical limit"? In some clinical trials for the so-called elderly women even those with 50 years of age were selected. However, the pure age is probably not the most important factor in the definition, because social, psychologic, financial, geographic status also play important roles in the definition of age as a complex overall status of health. Several individual differences may exist, and one should consider many other influencing factors. Most importantly "frailty" should be taken into consideration. Frailty encompasses a biologic syndrome of decreased reserve and resistance to various stressors, causing

vulnerability to adverse outcomes (2). Frail patients are at a higher risk for falling, disability, dementia, hospitalization, and death. One of the main causes is the progressive loss of hemostatic reserve. Before the development of the clinical syndrome of frailty, the patients still have sufficient reserve to cope with different noxae, before this pre-frail situation turns into a full frail status which will influence the outcome of various therapies. Specific noxae such as traumatic injury, stress or even a new disease like cancer or initiation of a therapy like chemotherapy can trigger the transition from a pre-frail state to a full-frail-state, leading to unexpected or more severe side effects. Frailty can greatly influence the treatment decision making process by cancer patients. Comorbidity is also another important factor in the treatment decision making process. Not only special illnesses contribute to the patients' ability to cope with cancer or anticancer therapy, but also the functional state, cognitive impairment or the nutritional status may lead to the extension of the hospitalization period and may affect the prognosis of patients (3). Social support and specific care are beneficial for the patients' prognosis and quality of life as well (4).

One of many useful methods to quantify the general condition of the elderly patient is the comprehensive geriatric assessment (CGA), an interdisciplinary process and score to diagnose and determine the patients' status to quantitatively assess life expectancy. CGA considers several categories like the typical geriatric syndromes, all relevant comorbidities, nutritional status, physical function and socioeconomic status. The application of the CGA in elderly breast cancer patients enables the clinicians to better assess their medical status and effectively decide over personalized therapeutic interventions and at the same time predict potential side effects or prognosis. It is also possible to point out situations where geriatric intervention may reverse or improve the patients' condition allowing for better therapy decisions and success.

CGA can be time consuming and could waste a great amount of medical resources. Screening tools such as, the most validated Geriatric8 (G8) can aid the selection of patients who possibly need a more in-depth analysis (4). A two-step approach from the geriatric oncology task force (5) can optimize the assessment of older cancer patients using G8 as a screening tool and first step before any relevant therapeutic decision. Patients who do not achieve a "fit status" will undergo as a second step, the gold standard CGA, otherwise the „fit patients "can be treated like the younger patients according to the established treatment guidelines.

For "unfit" patients special considerations should be made either to enhance their status to suit those treated like younger patients or when it is not possible to further optimize their cancer therapy to provide relief and improving quality of life.

Operation

The type of surgery of breast cancer is a well-discussed issue. Breast conserving surgery (BCS) followed by adjuvant radiation therapy (RT) is comparable to mastectomy in most relevant endpoints, however, patients after BCS are more satisfied with overall cosmetic outcomes when compared to mastectomy with either autologous or implant-based reconstruction surgery (6,7). Relevant factors for the decision-making process between BCS or mastectomy are Stage, breast size, age or comorbidity, but the surgeon's opinion or even the geographic distance or availability to radiation therapy facilities can also play a role. Generally, while BCS + RT is the preferred treatment for more than 60% of the woman, nevertheless in older woman mastectomy is often the preferred choice (8-11).

Irradiation techniques

Many types of radiotherapy are implicated in the therapy of breast cancer. The standard technique with respect to the breast irradiation remains the percutaneous whole breast irradiation by means of a linear accelerator. The 3D-conformal planning is mostly used for the application of a homogenous dose distribution and the optimal protection of the organs at risk (OAR) like lung or heart. Volumetric modulated arc therapy (VMAT) or Intensity-modulated radiation therapy (IMRT) techniques can be used in special anatomical constellations such as funnel chest or for mammaria interna irradiation.

The percutaneous irradiation of the breast is the most used radiation technique in the adjuvant setting whereby different fractionations can be applied. The standard therapy with "normofractionation" consists of up to 30–35 fractions with potential boost (sequential or simultaneous) with a daily dose of 1.8–2.0 Gy. In contrast, hypofractionation is implemented in only 15–16 fractions with a daily dose of 2.5–2.66 Gy. It has been already reported that this shorter or faster modality is not inferior in local- or locoregional control as well as in survival as the normal fractionation scheme and it was even superior regarding the acute side effects. The standard

fractionation regime is still widely in use perhaps because of a better funding in some countries (12).

Partial, or accelerated partial breast irradiation, as an additional percutaneous radiotherapy technique, (for e.g., 5×6 Gy) may be performed after the complete tumor excision following BCS; the radiation zone is limited to the operation area or tumor bed. However, in one meta-analysis it has been reported that the in-breast recurrences are significantly higher after partial breast irradiation (13) and it was discussed to have no statistical significantly difference in overall survival compared to no irradiation at all (14). Nevertheless, this method seems to be another reasonable option to improve local control for patients with needs for a rapid therapy course.

In the local treatment of breast cancer various brachytherapy techniques can be used either as a boost or as a single modality postoperative radiation. Regardless of the dose rate, the main purpose of this type of radiation is to protect the skin and the subcutaneous vessels from high radiation dose. The therapies are carried out either with multi-catheter brachytherapy applicator tubes placed in the area of the tumor bed during or after the tumor resection surgery; or with balloon brachytherapy, in which the balloon with a central brachytherapy catheter which is placed during the operation ("open cavity"), but also subsequently ("closed cavity") are introduced into the wound cavity. There were no relevant differences in outcome found between multicathetic or balloon brachytherapy in the different clinical studies performed. An optimal brachytherapy is ensured by the implementation of online planning, the preoperative diagnosis and imaging as well as the intraoperative status (clip marking of the tumor bed) and postoperative histology with the consideration of the respective resection margins. The exact target volume should include the tumor bed with a 2–3 cm safety margin in all directions with the multi-catheter technique or multi-channel balloon applicators. The target volume for the balloon-catheter with single-channel applicator is defined with 1 cm safety margin from the balloon surface. The treatment of tumor bed volumes above 200 cm^3 should be avoided. The optimal distance from the ribs and the skin should be minimum 5–7 mm in multi-catheter technique. These techniques may also be considered for the treatment of already irradiated patients in case of local tumor recurrence (15-17).

Many studies comparing the different radiation boost techniques showed a significantly lower recurrence rate with a factor of 2 to 3.25 for brachytherapy in relation to percutaneous radiotherapy (18-21). The boost application consists of a total dose with usually 8–13 Gy in 1–2 fractions and should begin within 1–2 weeks after the completion of percutaneous radiotherapy. For the application as single modality the therapy can take place as continuous LDR brachytherapy of 45 Gy over 4 days or fractionated HDR-brachytherapy of 32 Gy in 8 fractions or 34 Gy in 10 fraction each given twice daily. The experts of the ASTRO or the GEC-ESTRO found in various clinical studies that the 5-year recurrence rate was 0.9% for external beam radiation therapy and 1.4% for the APBI as the sole RT modality (P=0.42). The overall survival was 95.6% for external beam radiation therapy and 97.3% for partial breast irradiation (P=0.11). They defined the patient group for which a partial breast irradiation represents a good therapeutic alternative (17,22-24), namely: >50 years, tumor size <3 cm, grading 1–3, resection margins >2 mm, no multicentricity or multifocality, pN0, no extensive intraductal component, no neoadjuvant chemotherapy, histologically no lobular or solely *in situ* carcinoma. The relevant contraindications to interstitial boost are: T4 tumors, breast infection, multicentricity, as well as boost volumes over 150–200 cm^3 (for clips wide apart or large seromas).

Brachytherapy can be an attractive therapy alternative especially for elderly patient with low risk breast cancer, which typically takes place as in-patient over a few days with sometimes multiple daily radiation (e.g., twice a day), but single fraction application was also reported (25).

The intraoperative radiotherapy (IORT) is carried out immediately after the surgical tumor extirpation as a single treatment of the tumor resection cavity with application of a curative considered total dose (about 20 Gy). For an IORT, electrons of a linear accelerator (= IOERT), an orthovoltage therapy with 50 kV X-rays of a miniature X-ray machine or a balloon brachytherapy technique are used. The advantage of this therapy is that it completes the patients' quasi invasive treatments already in the operation setting. As a major disadvantage of this method it can be considered that a full pathological report is not yet available, hence the completeness of the treatment relies on the data collected by the sampling biopsy.

A supplemental dose for the tumor bed after or during the whole breast irradiation, also called boost, can further reduces the risk of breast cancer recurrence but does not seem to have any effect on overall survival up to 20 years out after treatment (26-30). This local therapy is directed to a coned-down volume of breast tissue consisting of the

tumor bed plus a 2- to 2.5-cm margin whereby an additional 10–16 Gy is delivered. Two randomized trials compared standard fractioned whole breast irradiation with or without tumor bed boost (28,31-33).

Both trials confirmed a lower risk for breast cancer recurrences in the arm treated with the boost dose. In the trial from European Organization for Research and Treatment of Cancer (EORTC) received 16 Gy supplemental dose and the greatest benefit was noted in younger patients. However, patients in all age categories achieved a statistically significant benefit for local control. According to the EORTC trial disadvantages of using a boost following whole breast radiation besides the longer treatment time is a higher rate of soft-tissue fibrosis and a higher probability of having less than a good/excellent cosmetic outcome. Nevertheless, boost should be recommended in the majority of the elderly patients as well, especially for those with high-risk cancer types, close margins, or an extensive intraductal component of the disease.

Indication of the radiation therapy

Evidence exists that women of all ages with triple negative breast cancer (34) or human epidermal growth factor receptor 2 (HER2) positive breast cancer (35) benefit from adjuvant RT concerning overall survival. Therefore, this type of adjuvant treatment is strongly recommended in high risk breast cancer even in elderly women where the life expectancy reaches 5 years (14).

Mortality of early stage breast cancer is considered to be low and short courses of RT over 3–4 weeks are generally as effective as longer courses. Hence, shorter treatment schemas are implicated in patients with Stage I, estrogen receptor positive, HER2 negative cancer with low KI67 (MIB-1) values. It has been recently shown that not only geographic proximity to treatment facilities, but even seasonal weather could play a role in the treatment decision for early-stage breast cancer (36,37).

A study from 2001 has determined that women younger than 70 years of age were twice as likely to receive radiation therapy after BCS as older women (38). In another study, only 45% of women older than 70 years received radiation after lumpectomy; the oldest group of women had radiation only 40% of the time after BCS (39). Nevertheless, a subgroup of patients where the adjuvant breast irradiation can be avoided after BCS has not been consistently identified (40).

Not accomplishing radiation therapy after BCS, or as an alternative the more frequent use of mastectomy should suppose to maintain a better quality of life and avoid side effects in patients with reduced life expectancy. It has been shown that the omission rates of irradiation can reach up to one third of the elderly patient's population after BCS (41). Interestingly, tumor grade, tumor size or pathological type didn't influence the clinical decision, but age over 80 years or missing pathological node evaluation did. It appears that best clinical judgment played an important role when deciding which patients were treated with radiation.

Despite of the numerous techniques, radiation therapy is sometimes considered as controversial treatment in the elderly patients. Fear from side effects, from tolerability or principally only from the modality can lead to reduced application of irradiation and not only limited for the low risk cases. Skin changes, erythema and ulcers have created a bad reputation amongst patients and semi-professional health care members. This side-effect is caused by the decreased tolerance of the skin to radiation burden and although earlier very common, with the advances of radiation techniques its prevalence decreased significantly and was not found to be influenced by the patient's age.

Special positioning techniques also allow for better control not only over the skin reaction (42) but also over the lung exposure (43). Further, the implementation of respiratory gating technique can also be beneficial for the OAR (44). Unfortunately, more complex patient positioning, increased treatment time and the cooperation of the patient are required and those are by elderly sometimes insufficiently feasible. It was found, that the risk for myocardial infarction or cardiovascular disease was not increased even without gating techniques, but at the same time the percutaneous breast irradiation was well tolerated among older women (45,46).

Endocrine therapy

Adjuvant endocrine therapies including anti-estrogen or aromatase inhibitors significantly reduce the chance of recurrence by approximately 40% and the likelihood of death by approximately 30% (47-50). This relative risk reduction is independent of the patient's age, tumor status, and prior therapy. Hence, when applicable, it is a valuable therapy option for patients with estrogen receptor positive breast cancer of all stages. Tamoxifen is a potent antiestrogen and is often considered to be the gold standard endocrine therapy for all stages of breast cancer (50). In high-risk breast cancer (stage II or III) it was found that

locoregional recurrence occurred in 8% of the radiotherapy plus tamoxifen group as compared to 35% of the tamoxifen only group; similarly, overall survival was also higher in the radiotherapy group with 45% *vs.* 36% at 10 years respectively (51). However, in patients with early stage, estrogen receptor (ER) positive breast cancer, it may be reasonable to abstain from irradiation when an endocrine treatment is available (52).

Fyles *et al.* analyzed the different adjuvant therapies of elderly patients with Stage I–II breast cancer and found that the rate of local relapse at five years was 7.7 percent in the tamoxifen group in contrast to 0.6 percent in the group which underwent tamoxifen plus irradiation, in a subgroup with T1, receptor-positive tumors the local relapses were 5.9% or 0.4% respectively, however without any significant difference in the rates of distant relapse or overall survival (35). Furthermore, neoadjuvant tamoxifen was proven to be an effective treatment option for elderly or frail patients with locally advanced estrogen receptor positive breast cancer with reasonable response rates (83% and 59% overall survival at 2 or 5 years respectively), and even cases with complete responses (53). These results indicate, that the combined adjuvant irradiation and endocrine therapy are very powerful means in improving the local control and even survival.

For the elderly or frail patients in low risk breast cancers the omission of adjuvant irradiation could be considered. The personal preferences of these patients could make the difference in the therapy decision-making process. Namely, possible short course irradiation with conceivable Grade I skin erythema or pain, compared to 5 years lasting possible side effects of the endocrine therapy like fatigue, joint pain, heat waves or osteoporosis; or even none of those but increased risk of recurrence.

Decision making

After the completion of tumor staging the appropriate therapy strategy should be always established involving the patient. Individual counselling is of great importance. After the assessment of the patient's general clinical condition according to the two-step approach proposed by the geriatric oncology task force group (5) the therapy decision can take place with the additional use of in silico prognostication algorithms, including but not limited to the two freely accessible online prediction algorithms application. These tools are designed to project the potential treatment benefit and to help clinical professionals and patients to make informed decisions about different treatment following breast cancer surgery and have been successfully tested on data from a great number of patients (54-56). After these procedures it is possible to choose an optimal, but yet sufficient therapy stated by the current guidelines.

Conclusions

Breast cancer usually affects older women and its incidence is expected to rise further over the next decades. Radiation therapy is an important modality in the therapy of breast cancer to reduce local recurrence and improve survival. Recent advances in the field of oncology, diagnostic and therapies allow for more options in the therapy design. Relevant to radiation therapy it can be concluded, that older patients with reasonable life expectancy should strived to be managed like younger ones; for patients with a life expectancy of less than 5 years, in high risk cases an adjuvant breast irradiation should always be offered, while in low risk cases the omission of the adjuvant irradiation can be a good therapy option in the majority of the cases.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Vincent Vinh-Hung and Nam P Nguyen) for the series "Radiotherapy for Breast Cancer in Advanced Age" published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.48). The series "Radiotherapy for Breast Cancer in Advanced Age" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Szigeti A, Szigeti E, Grajda A. Radiation therapy for the elderly—change of concepts in breast cancer? Transl Cancer Res 2020;9(Suppl 1):S131-S138. doi: 10.21037/tcr.2019.06.48

