



Stereotactic radiation therapy for breast cancer in the elderly

Pauline Jardel¹, Emmanuel Kammerer², Hugo Villeneuve¹, Juliette Thariat^{2,3}

¹Department of Radiation Oncology, Centre Intégré Universitaire de Santé et des Services Sociaux du Saguenay-Lac-St-Jean, Chicoutimi, Québec, Canada; ²Department of Radiation Oncology, Centre François Baclesse/ARCHADE, 14000 Caen, France; ³Laboratoire de physique corpusculaire IN2P3/ENSICAEN - UMR6534 - Unicaen - Normandie Université, France

Contributions: (I) Conception and design: P Jardel, J Thariat; (II) Administrative support: P Jardel, J Thariat, H Villeneuve; (III) Provision of study materials or patients: P Jardel, E Kammerer, J Thariat; (IV) Collection and assembly of data: P Jardel, E Kammerer; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Juliette Thariat. Department of Radiation Oncology, Centre François Baclesse/ARCHADE, 3 Av General Harris, 14000 Caen, France. Email: jthariat@gmail.com.

Abstract: The management of breast cancer in elderly women is going to be a major public health issue in a near future. The use of hypofractionated stereotactic radiotherapy is expanding but might be *a priori* not offered to older patients. We addressed the role of stereotactic radiotherapy (SBRT, 1–10 fractions) in elderly patients with breast cancer, in definitive, adjuvant and metastatic settings. Review of the literature. Of six series using SBRT for partial breast or breast boost irradiation and over 20 oligometastatic (brain, lung, liver, bone) SBRT series including patients aged ≥ 60 years old, no difference was found in term of efficacy (>80%) and toxicity (<5% G3-4) compared to the younger. Hypofractionation is also well adapted to the elderly, due to limited transportation-related fatigue. SBRT studies by age group are lacking. However, hypofractionated SBRT is particularly adapted to older patients with breast cancer, in term of efficacy and tolerability and should be encouraged rather than more morbid treatments whenever possible.

Keywords: Elderly; stereotactic; radiotherapy; breast cancer; oligometastatic; hypofractionation

Submitted May 31, 2019. Accepted for publication Jul 02, 2019.

doi: 10.21037/tcr.2019.07.18

View this article at: <http://dx.doi.org/10.21037/tcr.2019.07.18>

Introduction

Cancer is a disease of genes and increases with age. Because the elderly population is increasing, the treatment of cancer is becoming a major public health issue. The World Health Organization describes elderly people as people aged 60 years and over. This threshold in oncology is more commonly around 70 whereas people 80 years old and over are considered as the very elderly population (1-3). It is often used to guide therapeutic decisions. However, age should not be the sole criterion because of inter-individual variability in ageing processes (4). It is also important to understand the difference between life-expectancy and longevity: the first is societal but evolves with age, its statistical definition being based on the year of birth and demographic factors (including gender), whereas the second refers to individual factors, mainly genetics and lifestyle. In

a developed country like Canada, between 2013–2015, the lifespan at birth was 79.8 years for men and 83.9 years for women. But a man who has already reached the age of 70 has 15.4 other years of life-expectancy and a woman 17.9. At 90 years, it is 4.4 years for men and 5.2 years for women (5).

The relative risk of breast cancer increases by around six times in women aged 65 and more compared with younger women, and around one third of all new diagnosed breast cancer are aged 70 years and older (4). The management of breast cancer in elderly women is going to be a major public health issue in a near future. Elderly are less frequently treated with curative strategies (6) because they are believed to be more vulnerable to treatment-related toxicities. Combination of unfavorable factors is more likely to be met in older patients but physicians must not have preconceived opinion on a date of birth: a general assessment of the performance status, general prognosis,

medical history and medication intakes, wishes and beliefs and social conditions is mandatory before choosing the best personalized therapeutic strategy.

The concept of hypofractionated image-guided radiotherapy [SBRT (stereotactic body radiotherapy) or SABR (stereotactic ablative radiotherapy)] was first developed in intracranial lesions and further extended to extra cranial cancer localizations. The principle is to deliver a very high dose of radiotherapy in a small volume (margins are reduced) and in a few fractions (1 to 10 fractions). Such regimens limit transportation-related fatigue and are particularly adapted for the elderly. SBRT requires the same accuracy: precision in positioning, effective immobilization devices, image guidance and management of external and internal movements. It is better tolerated than conventional radiotherapy with hardly any acute toxicity and very few late effects usually below 5% for severe toxicities. Of note, elderly patients are under-represented in clinical oncological trials and SBRT trials.

The biological effects of SBRT are estimated from mathematical equations defined for doses per fraction <8 Gy but the high SBRT dose-range efficacy relies on additional cellular and tissular effects on cell membranes and vascular damages than DNA-molecular damages (7,8). SBRT efficacy may also rely on the abscopal effect, where out-of-fields tumors are treated through enhancement anti-tumoral immune response by ablative SBRT doses (9,10).

SBRT is increasingly used in various clinical settings despite little level of formal evidence (11). Whether SBRT is relevant in the elderly for the treatment of oligometastases appears consensual (12) with age as a minor criterion while general status is an important one.

The current review of the literature focuses on SBRT studies including elderly patients, and addresses tolerance and feasibility issues as well as clinical and logistic advantages that make SBRT especially attractive in the elderly.

Materials and method

We searched PubMed with the following keywords, in different combinations: “elderly”, “stereotactic”, “breast cancer”, “SBRT”, “oligometastatic”, “radiosurgery”, “hypofractionation”. The search was limited to articles published between 1990 and 2019 in peer-reviewed journals and in French and English languages. We additionally identified articles through selected authors own bibliographies.

Results—part 1: stereotactic irradiation of the breast

Local recurrences after conservative breast surgery occur within 2 cm of surgical margins in 80–85% of cases («tumor bed») (13-15). This finding suggests that partial breast irradiation, with various boost techniques (SBRT, brachytherapy, intra-operative radiotherapy...) is relevant in low-risk early breast cancer. To that extent, elderly women are often eligible. In a study published in 2005, Freedman *et al.* analyzed retrospectively the long-term risk of recurrence after whole-breast irradiation for 1,990 women with Tis-T1-T2 ductal carcinomas: recurrence outside the original quadrant where rare for the first 10 years (1–2%) but increased to 6% at 15 years. In this study, 18% of the patients were aged 70 or more and this group had lower rates of local recurrences whether in the tumor bed or elsewhere [2% at 15 years (0–5)] in the breast compared to the overall population. Thirty-four percent of patients received adjuvant systemic tamoxifen. Authors concluded that this result may indicate a therapeutic effect of whole-breast radiation for other areas of the breast. However, the very low rate of recurrence at 15 years is another argument to select elderly women for SBRT.

Adjuvant setting

The first SBRT studies in the management of early stage breast cancer were post-operative studies. SBRT was used either as a boost, or for accelerated partial breast radiation therapy (*Table 1*). Age was not an exclusion criterion, but mean ages were under 65 years. The proportion of patients aged >65 years were not given. SBRT has not yet been studied specifically in elderly patients who paradoxically most often have tumors with better histoprognostic factors than younger women.

Vermeulen *et al.* analyzed partial breast irradiation with Cyberknife (Accuray). Patients were randomized in two distinct groups: either a treatment planning with 30 Gy in 5 fractions (group 1), or 34 Gy in 10 fractions (group 2). Neither lung toxicity nor acute dermatitis was reported in either group. Only grade 1 edema in the breast was reported (17). Another Cyberknife study by Lozza *et al.* with the same dose and number of fractions included 20 patients with T1-T2aN0 invasive ductal carcinoma. Grade I erythema and edema occurred in respectively 20% and 30% of the cases, but were transient. Grade I fibrosis occurred in almost 60% in the cases, but in most cases disappeared

Table 1 SBRT studies in early breast cancer

| Author | Patients | Dose | Toxicities | Local control rates | PFS | Follow-up | Age (years) |
|---------------------|----------|---|--|---------------------|------|------------------------------|--------------------|
| Bondiau (16) | 28 | Conventional whole breast irradiation (50 Gy, 25 f) + single dose SBRT 8 Gy | 7% grade 2 toxicity. No grade >3 toxicity | 96% | 93% | 38 months (21.3–69.1 months) | 60.5 (43–82 years) |
| Vermeulen (17) | 9 | 30 Gy, 5 f; 34 Gy, 10 f | 44% grade 1 edema. No acute lung toxicity | - | - | 7 months (4–26 months) | 56 (46–68 years) |
| Lozza (18) | 20 | 30 Gy, 5 f | No > grade 2 skin toxicity. No acute lung toxicity | 100% | 100% | 27.7 months (25.7–32.0) | More than 45 |
| Obayomi-Davies (19) | 10 | 30 Gy, 5 f | No lung, heart, chest wall toxicity. 10% grade 1 late skin toxicity | 100% | 100% | 1.3 years | 61 (48–77 years) |
| Livi (20) | 260 | 30 Gy, 5 f | 18% grade 1 acute skin toxicity, 2% acute grade 2 skin toxicity. No grade 2 late skin toxicity. No other toxicity | 99% | 97% | 5 years | More than 40 |
| Rahimi (21) | 75 | 30 to 40 Gy, 5 f | 14.6% acute grade 1 dermatitis 1.3% acute grade 2 and 3 dermatitis. 13% fat necrosis. 12% late grade 1 hyperpigmentation | 100% | 100% | 26.1 months (4.4–56.1) | 62 (45–79 years) |

Gy, Gray; f, fractions; PFS, progression free survival.

after 6 months of follow-up. No grade ≥ 2 acute or late skin toxicities were observed, no lung toxicity was observed (18). Those studies concluded to a good feasibility and safety of stereotactic partial breast irradiation in early breast cancer. Similarly, a phase II study by Bondiau *et al.* for T1-T2N0 breast tumors included 28 patients treated by conventional whole breast irradiation (50 Gy, 25 fractions) and a single dose (8 Gy) SBRT boost to the tumor bed (16). One case of nodal relapse in an elderly woman and one case of local relapse (both with triple negative breast cancer) were reported during follow-up. At 3 months, there were 22 grade 1 cutaneous toxicities, including breast fibrosis, pain, erythema, and pigmentation. At 36 months, there were 5 grade I skin toxicities. SBRT in a few ambulatory fractions appears safe and adequate for elderly women. No age subgroup was identified as a limiting factor in the studies and elderly women are more likely the subgroup to benefit from partial breast irradiation.

Neoadjuvant SBRT

Whether breast conservation has not been specially studied in the elderly, it is quite common in standard practice that very elderly women refuse mastectomy. Neoadjuvant irradiation may be used to allow conservative breast surgery. Studies focusing on SBRT in the neo-adjuvant setting in early breast cancer are reported in *Table 2*.

Bondiau *et al.* performed a phase I dose escalation study of pre-operative SBRT associated with chemotherapy for patients who could not have breast-conserving surgery upfront (22). Chemotherapy consisted of 3 courses of docetaxel, 3 courses of fluorouracil, epirubicin, cyclophosphamide with concomitant SBRT, followed by surgery and conventional whole breast radiotherapy. Fiducial-based image-guided and SBRT was performed with respiratory tracking, at a dose of 19.5 to 22.5 Gy in 3 fractions. Six patients, mean age of 53 years (range, 34–67) had to be eligible to receive chemotherapy, thus limited eligibility in some elderly patients. Only one case of grade 1 skin toxicity (erythema) but no pulmonary toxicity was reported. Two patients had a pathological complete response and 4 a pathological partial response. SBRT allowed 5 patients out of 6 to receive conservative breast surgery instead of mastectomy. The subsequent study (23), used 5 different doses of 19.5, 22.5, 25.5, 28.5, and 31.5 Gy in 3 fractions in 25 patients. One patient experienced a grade 3 acute skin dermatitis. The pathological complete response was 67% at dose level 3, 43% at dose level 4, 33% at dose

Table 2 SBRT neo-adjuvant studies in early breast cancer

| Authors | Patients | Dose | Toxicities | Local control | Follow-up |
|--|----------|--|----------------------------|--|-----------|
| Bondiau 2009 (22) | 6 | 19.5 to 22.5 Gy, 3f + adjuvant conventional whole breast irradiation | No skin toxicity | 33% pathological complete response; 66% pathological partial response | – |
| Bondiau 2013 (23) | 25 | 19.5, 22.5, 25.5, 28.5, 31.5 Gy, 3 f | One grade 3 skin toxicity | 100% | 30 months |
| Blitzblau, Horton <i>et al.</i> 2015 (24-26) | 32 | Single dose: 15, 18, 21 Gy | No skin toxicity > grade 3 | – | 23 months |

Gy, Gray; f, fractions.

level 5. Lumpectomy was performed in 92% of patients, and no local recurrence occurred. 92% patients remained free of distant metastasis. This study proved the feasibility of pre-operative SBRT with the aim to make conservative surgery, without significant increase in acute toxicity. Blitzblau *et al.* studied SBRT in favorable prognosis breast cancer in a phase I of preoperative partial breast radiotherapy. Of 25 patients, 8 received a single dose of 15 Gy, 8 received 18 Gy, 16 received 21 Gy (26). Unlike Bondiau's study, only T1-T2N0 breast cancer patients with favorable histological patterns (estrogen or progesterone positive receptors, no lymphovascular invasion on biopsy) were included. Patients were treated in prone position. A fiducial placed during the biopsy allowed tumor tracking. No acute or late grade 3 or 4 skin, pulmonary or heart toxicity were related during the 23 months follow-up. Only grade I acute dermatitis, fibrosis, and skin hyperpigmentation were observed, in respectively 39%, 77% and 23% of the cases. No recurrence was reported in 23 months after treatment (12).

These studies suggest that SBRT is safe and effective in a neo-adjuvant setting. Long term data is currently missing, but this option should be considered as an option in elderly patients in order to avoid complete breast radiation therapy over three to five weeks. Conservative breast surgery may be more important from a patient standpoint in elderly women and very elderly women. However, data is limited and specific protocols may be needed with respect to chemotherapy.

Definitive radiotherapy

Few treatment options exist for elderly patients diagnosed with early stage breast cancer, of whom elderly are more likely to be medically unfit for surgery or to refuse surgery.

Hypofractionated 3D radiation therapy is commonly used but may have cardiac toxicity and should be avoided in elderly people with cardiac comorbidities (27). SBRT may limit the volumes of heart and lung irradiated. In patients undergoing exclusive breast radiation therapy, local and distant relapse-free rate have been published to of 56% and 33% at 5 years (28). Shibamoto *et al.* studied conventional whole breast irradiation followed by a boost of 18 to 25.5 Gy in 3 fractions using SBRT only in patients who had no sign of lymph node involvement on tomography with positron emission (29). Eighteen patients were included (5 patients with positive lymph node on PET-CT were treated with IMRT for nodal irradiation). Ages ranged from 32 to 80 years (median 48). No tracking was performed on the tumor (no fiducial markers). No grade >3 toxicity were observed. The median follow-up was 35 months. This study showed a local control rate of 92% at 3 years: only one patient relapsed and was initially diagnosed with a T3 breast tumor with lymphatic involvement. Very few of those studies reported indicators such a quality of life or fatigue. Rahimi *et al.* related acute and residual grade 1 fatigue in respectively 11% and 5% of the cases (21). Bondiau *et al.* reported no quality of life deterioration (assessed by the EORTC QLQ-BR23) during and after radiotherapy, and specifically for items specific to breast irradiation, which makes SBRT relevant in the elderly (14).

Definitive radiotherapy is standard practice in the elderly and irradiation even more in the very elderly. SBRT as a boost after whole breast irradiation or as partial in good has the potential to spare the heart and lungs better than 3D and IMRT. Studies of SBRT in early breast cancer, for the boost or exclusive partial breast irradiation, show safety and feasibility of the technique overall and in the elderly. SBRT may also be a good means to preserve the quality of life in the elderly.

Results—part 2: stereotactic radiation therapy for metastases

Thirty to 40% of patients with breast cancer develop distant metastases (30). The standard of care relies on systemic therapies with chemotherapy and/or hormonal therapy. Despite increasing efficacy of modern drugs, only few patients treated with systemic treatment maintain durable disease control and treatments follow one another: median survival in recurrent breast cancer is around 33–38 months in recent studies (57% if the estrogenic receptor is expressed, 33% if not) and 31 months for *de novo* stage IV (31). The question of the intrinsic prognosis (regardless of treatments) in elderly women with metastatic breast cancer is debated. Poorer general prognosis has been reported, in part, due to more advanced stage, because of delayed diagnosis in this age group (32). Others have reported worse outcomes due to increased metastatic propensity (33,34) and hypothesized aging immune defense mechanisms in the elderly. Decline in stem cells, B-cell dependent antibody response, T-lymphocyte production, activities of neutrophils, macrophages and natural killer cells have been reported with age. While the immune function is maintained in normal conditions, it may be overflowed with neoplastic processes (35). On the other hand, older patients more likely have favorable biological tumor types, which overexpress hormonal receptors, rarely overexpress HER2, and are usually less proliferative and with little vascular peritumoral invasion (36).

SBRT in the metastatic setting is used either upfront or as consolidation after systemic treatments when the metastatic disease is limited to oligometastatic bulk. Oligometastatic disease refers to an early stage in the spectrum of the metastatic disease in which the neoplastic mass can be addressed locally (37). Typically, it concerns patients with one to 5 macroscopic-radiographically detected metastases (38). Oligometastatic breast cancer is a distinct subgroup with long-term prognosis superior to the entire group of metastatic breast cancer, and clinical cure may be aimed at (39). Different situations are described: (I) oligo-recurrence defines the case of a controlled primary tumor with a limited number of metastases (40); (II) oligoconsolidation describes a polymetastatic disease that is under control, except for some metastatic sites (<5) that do not respond as well to systemic treatment as the others; (III) oligoprogression defines the case of a globally progressive polymetastatic disease, but with a small (<5) number of metastases growing faster than the other and potentially

symptoms-taker (37,41). The prognosis decreases from (I) to (II) to (III) (41). This definition seems to be even more relevant as systemic therapies are increasingly effective, and stereotactic radiotherapy is now proposed in aggressive metastatic situations. Foci of macroscopic disease are aggressively treated for durable local control and probably for increased overall outcomes. As for the elderly population, a SEER population-based analysis in the period 2010–2013 on 4,932 metastatic breast cancer patients revealed that elder stage IV patients were less likely to have multiple metastatic sites than younger women ($P<0.001$) (3). In the elderly, because of the excellent tolerance of a few SBRT fractions compared to the tolerance to systemic treatments, SBRT is particularly promising in all the above-mentioned oligometastatic situations.

Brain metastases

Breast cancer is the second most frequent cause of brain metastasis. Incidence of symptomatic brain metastasis is estimated to be around 15% and is detected earlier. Young age, negative estrogen receptor, and HER2 protein overexpression are poor risk factors for brain metastases in breast cancer patients (42–44). Because breast cancer patients live increasingly longer and brain metastases occur at late stages of the metastatic process, detection in elderly patients is a growing issue. Brain metastasis-related symptoms affect the quality of life (pain, higher neurological functions like language, praxis, reasoning and personality, coordination, power, sensitivity...) in a way that is even more critical to the elderly, because of their low capacity to cope with new disabilities. Whole brain irradiation has been shown to deteriorate cognitive functions even more dramatically after 60 years old and SBRT thus should be privileged in this population. The Graded Prognostic Assessment score (GPA), the diagnosis-specific GPA and the Recursive partitioning assessment score (RPA) (45–47) are based on clinical characteristics such as performing status, extension of the extracranial disease, primary tumor type, number of metastases and age (46) and can be used to guide treatment (45,48–53). Whole brain irradiation is also responsible for acute alopecia, which is often considered as a benign side-effect but may affect self-esteem and body image. Chang *et al.* (MD Anderson 2009) reported however a significant difference in OS between patients receiving SBRT and WBRT + SBRT (respectively 15.2 and 5.7 months, $P=0.02$; breast cancer was the primary tumor in 14% of patients and median age was 64–65 years old) (53,54). In a retrospective

study of 119 elderly patients with 811 brain metastases from solid malignancies including breast cancer treated with SBRT or WBRT (55), elderly aged 70–79 years and very elderly ≥ 80 years did not have significant difference in acute toxicities rates, suggesting that age alone might not be such a relevant point in therapeutic decision making. However, WBRT increased cognitive deterioration and the decrement of quality of Life. The authors concluded that SRS should be better evaluated in the geriatric population to minimize treatment-related toxicity. This is particularly true in view of the possibility to deliver a new course of SBRT in case of intracranial relapse.

Lung metastases

Long survivors can be observed after metastasectomy of lung metastases (56). Intriguingly, the SEER population-based analysis in the period 2010–2013 on 4,932 metastatic breast cancer patients revealed that elderly patients were more likely to have lung metastasis than younger women (3).

Because not all patients are subjected for surgical excision (57) due to comorbidities, which are more likely with older age, SBRT appears as a reasonable alternative to both systemic treatments and surgery (see review by the IGRG). Ricco *et al.* published a series of 577 patients treated with SBRT for lung metastasis with a 13 months follow-up (58). Breast cancer represented 9.2% of the group and the median age was 69 years (range, 18–93). No difference in local control was seen by primary tumor and no difference was reported according to age. The 3 year-OS for breast cancer patients was 47.9% and the 2-year local control 72.4%. SBRT appears as a relevant treatment of oligometastases from breast cancer in the elderly despite the absence of specific randomized studies.

Hepatic metastases

Liver is a common site of metastases in breast cancer and is associated with poor survival. The standard of care relies on systemic therapies. Local treatments include surgery, arterial chemoembolisation, radiofrequency ablation and SBRT. Surgery is invasive and can only be proposed in selected patients, considering its morbidity. Ahmed *et al.*, retrospectively study 372 liver metastasis and they developed a multigene expression model of tumor radiosensitivity for a total dose of 50–60 Gy in 5 daily consecutive fractions: liver metastasis from breast cancer were more radiosensitive than those from colorectal cancer (59). On the other hand,

Mahadevan *et al.* found no differences in local control based on the histology (60). Ohri *et al.* had excellent local control rates after SBRT for liver metastasis using total doses with BEDs >100 Gy₁₀ (61). A hypothesis is that heavily pretreated (like patients with colorectal cancer) patients may have more radioresistant metastases. SBRT allows for dose escalation in 3 to 5 fractions in liver metastases and is well adapted for aging people, less likely to have been exposed to systemic therapy than younger patients. SBRT does not require hospitalization and is less invasive than other local treatments. Side effects comprise rib fractures, duodenal ulcer but treatment-related death is not reported.

Bone metastases

Bone metastasis are the most frequent cause of pain in breast cancer patients and is successfully managed by conventional radiotherapy but may also be managed by SBRT (62–66). Other benefits from skeletal irradiation are bone reconstruction and consolidation, prevention of fractures and neurological lesions. Gagnon *et al.* published a series of 18 breast cancer patients treated with SBRT for bone metastases, in which 3 were aged 60–69 and one >70 years old (67). There were no differences according to age group. The single-dose of 8 Gy is easy to prescribe and is equivalent to the traditional 20–30 Gy for pain control, with however a shorter duration of pain control (65,68). Also, the use of SBRT has to be motivated by a better local control and/or tolerance compared to the «8 Gy-flash». In a systematic review, Spencer *et al.* (2,619 studies) concluded that both local control rates were high and pain responses were superior to those reported for conventional radiotherapy. Data were not specific to elderly breast cancer patients. However, SBRT for bone metastases from breast cancer in the elderly appears to have a good risk benefit ratio. Randomized studies are ongoing, and should provide subgroup analyses on elderly people.

Discussion

The management of older patients challenges radiation oncologists and is not well supported by the literature due to the absence of specific data. Therapeutic-decision groups often omit elderly patients, which indirectly leads to situations where the elderly is less likely to receive curative and/or the newest therapies than younger patients (4). There is high rate of non-compliance (64%) in octogenarians to adjuvant radiation therapy recommendations after

lumpectomy (69). There is no study evaluating the risk-benefit ratio of adjuvant radiation therapy in women over 80 years of age with breast cancer. Although, the CALGB 9343 trial included women aged 70 and more with stage I, estrogen receptor positive breast cancer and showed a difference at 10 years of 9% versus 2% of local recurrences respectively in the groups treated with hormonal therapy alone and hormonal therapy and whole-breast radiotherapy (70). The morbidity was higher in the radiation therapy group. There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or OS between the two groups. These results were confirmed by the PRIME study including women over 65 years: at 5 years, the local recurrence was 4.1% versus 1.3% with the adjunction of radiotherapy (71). These trials plead in favor of choosing a pauci-morbid and efficient radiotherapy modality, as SBRT could be.

Older patients may benefit from SBRT for 3 specific reasons:

- (I) Efficacy. Data specific to elderly people is lacking. However, series of breast cancer patients treated with SBRT and elderly were not excluded nor studied as subgroups. Results were excellent in terms of local control. The SABR-COMET study (phase II) compared SBRT in patients with a controlled primary tumor and one to five oligometastatic lesions to palliative standard treatments (including conventional radiotherapy). Patient ages were comprised between 59 and 75 years (median 67/69 years). Breast cancer represented 15% and 20% of patients in each group respectively. SBRT was associated with a 13-month improvement in median survival and a doubling of median progression-free survival. The study did not show however that SBRT increased the time to chemotherapy, which is less well tolerated than SBRT in the elderly and could accelerate frailty (72).
- (II) Tolerance and delayed side-effects of SBRT compared to conventional radiotherapy. SBRT is associated with less than 5% of long-term side effects and practically no acute complications. This is very important in elderly people who are at risk for accelerated frailty in such circumstances.
- (III) Quick-treatment-time. Transportation issues are a major break in therapeutic decisions. Elderly are more likely to be dependent of someone for transportation to the hospital. It is not so infrequent that the proposition of a conventional

daily treatment for one to five weeks is declined by the patient for many extra-medical reasons: they do not want to disturb family or friends, children could not drive because they are working, transportation could be really be complicated by limited mobility and the fear of living home. Furthermore, the medical transportation is not well organized in many countries and the price of the course might prevent patients from seeking radiation therapy. Of note, economic factors might also be important in aging population with financial and overall vulnerability. Homeostatic reserves are eroded in aging people and a stressor event might trigger major decline in health. The life-routine is highly structuring in elderly and breaking it with multiple travels to the hospital is a stressful event. Hypofractionated SBRT in general, including SBRT, appears to be suited for elderly cancer patients to reduce transportation issues and costs. Practically, with five SBRT fractions prescribed, the patient has to travel 7 or 8 times to the hospital, including the initial consultation. The number could reduce to 3 or 4 (consultation and dosimetric-TDM; fluoroscopy and verifications in treatment position; treatment). In comparison, a standard radiotherapy regimen includes up to 35 travels (1 consultation, 1 planning scanner, 25 treatment times and 4 to 8 additional fractions for the boost). Even with the English fractionation (40.05 Gy, 15 fractions, over 3 weeks), the total number of travels is minimum 16–17.

The medical evaluation of the patients is the cornerstone of the therapeutic decision and can be supported by the use of geriatric assessment tools. Circulating biomarkers of aging are increasingly being developed in current research and would help in a near future for personalized-medicine strategy, such as microRNAs (73). Interestingly, biomarkers of aging are also found in breast cancer survivors (reflecting higher DNA damage and lower telomerase activity), years after chemotherapy or radiation therapy, suggesting a long-lasting effect of treatments (74).

Conclusions

SBRT is less developed in breast cancer because systemic therapies are numerous and randomized trials lack for the comparison of adding a local treatment versus chemotherapy only. SBRT is however promising for elderly women with breast cancer: it provides comparable and even

superior outcomes compared to standard fractionation in selected populations with excellent tolerance and quick treatment-time (fewer transportations, less fatigue, fewer modifications of daily life-routine). Physicians should probably more systematically propose this technique in elderly patients and favor clinical trials that include elderly people.

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.2019.07.18>). 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Scotté F, Bossi P, Carola E, et al. Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. *Ann Oncol* 2018;29:1718-26.
2. Giugliano FM, Falivene S, Esposito E, et al. External radiotherapy for breast cancer in the elderly. *Aging Clin Exp Res* 2017;29:149-57.
3. Chen MT, Sun HF, Zhao Y, et al. Comparison of patterns and prognosis among distant metastatic breast cancer patients by age groups: a SEER population-based analysis. *Sci Rep* 2017;7:9254.
4. Popescu T, Karlsson U, Vinh-Hung V, et al. Challenges Facing Radiation Oncologists in The Management of Older Cancer Patients: Consensus of The International Geriatric Radiotherapy Group. *Cancers* 2019;11. doi: 10.3390/cancers11030371.
5. Gouvernement du Canada SC. Espérance de vie et autres éléments de la table de mortalité, Canada, toutes les provinces excepté l'Île-du-Prince-Édouard [Internet]. 2018 [cité 28 mai 2019]. Disponible sur: Available online: <https://www150.statcan.gc.ca/t1/tbl1/fr/tv.action?pid=1310011401>
6. Passage KJ, McCarthy NJ. Critical review of the management of early-stage breast cancer in elderly women. *Intern Med J* 2007;37:181-9.
7. Macià I Garau M. Radiobiology of stereotactic body radiation therapy (SBRT). *Rep Pract Oncol Radiother* 2017;22:86-95.
8. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys* 2014;88:254-62.
9. Thariat J, Boudabous M. [The abscopal effect, synergy between immunotherapy and radiotherapy]. *Bull Cancer (Paris)* 2013;100:1071.
10. Bernstein MB, Krishnan S, Hodge JW, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* 2016;13:516-24.
11. Lewis SL, Porceddu S, Nakamura N, et al. Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases: An International Survey of >1000 Radiation Oncologists. *Am J Clin Oncol* 2017;40:418-22.
12. Dagan R, Lo SS, Redmond KJ, et al. A multi-national report on stereotactic body radiotherapy for oligometastases: Patient selection and follow-up. *Acta Oncol* 2016;55:633-7.
13. Schnitt SJ, Hayman J, Gelman R, et al. A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. *Cancer* 1996;77:1094-100.
14. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. *Ann Oncol*

- 2001;12:997-1003.
15. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation using external beam conformal radiation therapy: a review. *Crit Rev Oncol Hematol* 2012;81:1-20.
 16. Bondiau P-Y, Gal J, Chapellier C, et al. Robotic Stereotactic Boost in Early Breast Cancer, a Phase 2 Trial. *Int J Radiat Oncol Biol Phys* 2019;103:374-80.
 17. Vermeulen S, Cotrutz C, Morris A, et al. Accelerated Partial Breast Irradiation: Using the CyberKnife as the Radiation Delivery Platform in the Treatment of Early Breast Cancer. *Front Oncol* 2011;1:43.
 18. Lozza L, Fariselli L, Sandri M, et al. Partial breast irradiation with CyberKnife after breast conserving surgery: a pilot study in early breast cancer. *Radiat Oncol* 2018;13:49.
 19. Obayomi-Davies O, Kole TP, Oppong B, et al. Stereotactic Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: Rationale, Feasibility, and Early Experience Using the CyberKnife Radiosurgery Delivery Platform. *Front Oncol* 2016;6:129.
 20. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015;51:451-63.
 21. Rahimi A, Thomas K, Spangler A, et al. Preliminary Results of a Phase 1 Dose-Escalation Trial for Early-Stage Breast Cancer Using 5-Fraction Stereotactic Body Radiation Therapy for Partial-Breast Irradiation. *Int J Radiat Oncol Biol Phys* 2017;98:196-205.e2.
 22. Bondiau PY, Bahadoran P, Lallement M, et al. Robotic stereotactic radioablation concomitant with neo-adjuvant chemotherapy for breast tumors. *Int J Radiat Oncol Biol Phys* 2009;75:1041-7.
 23. Bondiau PY, Courdi A, Bahadoran P, et al. Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2013;85:1193-9.
 24. Blitzblau RC, Horton JK. Treatment planning technique in patients receiving postmastectomy radiation therapy. *Pract Radiat Oncol* 2013;3:241-8.
 25. Horton JK, Blitzblau RC, Yoo S, et al. Preoperative Single-Fraction Partial Breast Radiation Therapy: A Novel Phase 1, Dose-Escalation Protocol With Radiation Response Biomarkers. *Int J Radiat Oncol Biol Phys* 2015;92:846-55.
 26. Blitzblau RC, Arya R, Yoo S, et al. A phase 1 trial of preoperative partial breast radiation therapy: Patient selection, target delineation, and dose delivery. *Pract Radiat Oncol* 2015;5:e513-20.
 27. Lemanski C, Thariat J, Ampil FL, et al. Image-guided radiotherapy for cardiac sparing in patients with left-sided breast cancer. *Front Oncol* 2014;4:257.
 28. Thomas F, Arriagada R, Mouriessé H, et al. Radical radiotherapy alone in non-operable breast cancer: the major impact of tumor size and histological grade on prognosis. *Radiother Oncol* 1988;13:267-76.
 29. Shibamoto Y, Murai T, Suzuki K, et al. Definitive Radiotherapy With SBRT or IMRT Boost for Breast Cancer: Excellent Local Control and Cosmetic Outcome. *Technol Cancer Res Treat* 2018;17:1533033818799355.
 30. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812-23.
 31. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. *JNCI Cancer Spectr* 2018;2:pk062.
 32. Botteri E, Bagnardi V, Goldhirsch A, et al. Axillary lymph node involvement in women with breast cancer: does it depend on age? *Clin Breast Cancer* 2010;10:318-21.
 33. Singh R, Hellman S, Heimann R. The natural history of breast carcinoma in the elderly: implications for screening and treatment. *Cancer* 2004;100:1807-13.
 34. Wildiers H, Van Calster B, van de Poll-Franse LV, et al. Relationship between age and axillary lymph node involvement in women with breast cancer. *J Clin Oncol* 2009;27:2931-7.
 35. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381:752-62.
 36. Le Saux O, Ripamonti B, Bruyas A, et al. Optimal management of breast cancer in the elderly patient: current perspectives. *Clin Interv Aging* 2015;10:157-74.
 37. Kissel M, Helou J, Thariat J. Definitions of oligometastatic disease and new treatment concepts. *Bull Cancer* 2018;105:696-706.
 38. Kobayashi T, Ichiba T, Sakuyama T, et al. Possible clinical cure of metastatic breast cancer: lessons from our 30-year experience with oligometastatic breast cancer patients and literature review. *Breast Cancer* 2012;19:218-37.
 39. Westphal T, Gampenrieder SP, Rinnerthaler G, et al. Cure in metastatic breast cancer. *Memo* 2018;11:172-9.
 40. Niibe Y, Chang JY, Onishi H, et al. Oligometastases/Oligo-recurrence of lung cancer. *Pulm Med* 2013;2013:438236.

41. Helou J, Thibault I, Poon I, et al. Stereotactic Ablative Radiation Therapy for Pulmonary Metastases: Histology, Dose, and Indication Matter. *Int J Radiat Oncol Biol Phys* 2017;98:419-27.
42. Duchnowska R, Biernat W, Szostakiewicz B, et al. Correlation between quantitative HER-2 protein expression and risk for brain metastases in HER-2+ advanced breast cancer patients receiving trastuzumab-containing therapy. *Oncologist* 2012;17:26-35.
43. Tham IWK, Hee SW, Yeo RMC, et al. Treatment of nasopharyngeal carcinoma using intensity-modulated radiotherapy—the national cancer centre singapore experience. *Int J Radiat Oncol Biol Phys* 2009;75:1481-6.
44. Gil-Gil MJ, Martinez-Garcia M, Sierra A, et al. Breast cancer brain metastases: a review of the literature and a current multidisciplinary management guideline. *Clin Transl Oncol* 2014;16:436-46.
45. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012;30:419-25.
46. Nieder C, Dalhaug A, Pawinski A. External Validation of the LabBM Score in Patients With Brain Metastases. *J Clin Med Res* 2019;11:321-5.
47. Miyazawa K, Shikama N, Okazaki S, et al. Predicting prognosis of short survival time after palliative whole-brain radiotherapy. *J Radiat Res (Tokyo)* 2018;59:43-9.
48. Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999;45:427-34.
49. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665-72.
50. Sperduto PW, Shanley R, Luo X, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). *Int J Radiat Oncol Biol Phys* 2014;90:526-31.
51. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006;295:2483-91.
52. Kocher M, Soffiatti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29:134-41.
53. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;10:1037-44.
54. Mazzola R, Corradini S, Gregucci F, et al. Role of Radiosurgery/Stereotactic Radiotherapy in Oligometastatic Disease: Brain Oligometastases. *Front Oncol* 2019;9:206.
55. Chen L, Shen C, Redmond KJ, et al. Use of Stereotactic Radiosurgery in Elderly and Very Elderly Patients With Brain Metastases to Limit Toxicity Associated With Whole Brain Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2017;98:939-47.
56. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37-49.
57. Nguyen NP, Godinez J, Shen W, et al. Is surgery indicated for elderly patients with early stage nonsmall cell lung cancer, in the era of stereotactic body radiotherapy? *Medicine (Baltimore)* 2016;95:e5212.
58. Ricco A, Davis J, Rate W, et al. Lung metastases treated with stereotactic body radiotherapy: the RSSearch® patient Registry's experience. *Radiat Oncol* 2017;12:35.
59. Ahmed KA, Caudell JJ, El-Haddad G, et al. Radiosensitivity Differences Between Liver Metastases Based on Primary Histology Suggest Implications for Clinical Outcomes After Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2016;95:1399-404.
60. Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. *Radiat Oncol* 2018;13:26.
61. Ohri N, Tomé WA, Méndez Romero A, et al. Local Control After Stereotactic Body Radiation Therapy for Liver Tumors. *Int J Radiat Oncol Biol Phys* 2018. [Epub ahead of print].
62. Jabbari S, Gerszten PC, Ruschin M, et al. Stereotactic Body Radiotherapy for Spinal Metastases: Practice Guidelines, Outcomes, and Risks. *Cancer J* 2016;22:280-9.
63. Chang JH, Shin JH, Yamada YJ, et al. Stereotactic Body Radiotherapy for Spinal Metastases: What are the Risks and How Do We Minimize Them? *Spine* 2016;41 Suppl 20:S238-45.
64. Spencer K, van der Velden JM, Wong E, et al. Systematic review of the role of stereotactic radiotherapy for bone

- metastases. *J Natl Cancer Inst* 2019. [Epub ahead of print].
65. Chow E, Zeng L, Salvo N, et al. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* 2012;24:112-24.
 66. Foro Arnalot P, Fontanals AV, Galcerán JC, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiother Oncol* 2008;89:150-5.
 67. Gagnon GJ, Henderson FC, Gehan EA, et al. Cyberknife radiosurgery for breast cancer spine metastases: a matched-pair analysis. *Cancer* 2007;110:1796-802.
 68. Sze WM, Shelley M, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials. *Cochrane Database Syst Rev* 2004;(2):CD004721.
 69. Strader LA, Helmer SD, Yates CL, et al. Octogenarians: noncompliance with breast cancer treatment recommendations. *Am Surg* 2014;80:1119-23.
 70. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-7.
 71. Kunkler IH, Williams LJ, Jack WJL, et al, PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015;16:266-73.
 72. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051-8.
 73. Dalmasso B, Hatse S, Brouwers B, et al. Age-related microRNAs in older breast cancer patients: biomarker potential and evolution during adjuvant chemotherapy. *BMC Cancer* 2018;18:1014.
 74. Scuric Z, Carroll JE, Bower JE, et al. Biomarkers of aging associated with past treatments in breast cancer survivors. *NPJ Breast Cancer* 2017;3:50.

Cite this article as: Jardel P, Kammerer E, Villeneuve H, Thariat J. Stereotactic radiation therapy for breast cancer in the elderly. *Transl Cancer Res* 2020;9(Suppl 1):S86-S96. doi: 10.21037/tcr.2019.07.18