



Original article

Portrait, treatment choices and management of breast cancer in nonagenarians: An ongoing challenge



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ABSTRACT

There are only scarce data on the management of nonagenarians with breast cancer, and more particularly on the place of radiation therapy (RT). We report a retrospective study on patients aged 90 years old or older, with breast cancer, receiving RT.

Records from RT departments from five institutions were reviewed to identify patients 90 years old of age and older undergoing RT over past decade for breast cancer. Tumors' characteristics were examined, as well treatment specificities and treatment intent.

44 patients receiving RT courses were identified, mean age 92 years. Treatment was given with curative and palliative intent in 72.7% and 27.3% respectively. Factors associated with a curative treatment were performance status (PS), place of life, previous surgery, and tumor stage. Median total prescribed dose was 40 Gy (23–66). Hypo fractionation was used in 77%. Most toxicities were mild to moderate. RT could not be completed in 1 patient (2.3%). No long-term toxicity was reported. Among 31 patients analyzable for effectiveness, 24 patients (77.4%) had their diseased controlled until last follow-up, including 17 patients (54.8%) experiencing complete response. At last follow-up, 4 patients (12.9%) were deceased, cancer being cause of death for two of them.

The study shows that breast/chest RT is feasible in nonagenarians. Although the definitive benefit of RT could not be addressed here, hypofractionated therapy allowed a good local control with acceptable side effects.

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Introduction

Breast cancer is a major source of morbidity and mortality in elderly women and an increasing healthcare issue [1,2]. The number of persons aged 90 or more in the world has increased significantly over the last two decades: from 6.714 million people in 1995, their number rose from 12.15 million people in 2013. Two-thirds of those over 85 are women [3]. In the US population,

breast cancer is relatively common among women age >80 years and older with nearly 400 cases per 100 000 women [4]. Despite the high incidence, few data are available on breast cancer characteristics, treatment choices, and survival for women age 90 years or older [5]. There is a lack of evidence on the optimal management of this group of patients because of their low enrollment in randomized clinical trials [6,7]. Treatment decisions have been largely based on studies in younger patients, which may not be applicable to nonagenarians with breast cancer. Due to their geriatric vulnerability and lack of specific guidelines, elderly breast cancer patients receive frequently less aggressive adjuvant therapies, even for node-positive cases [8–11]. Despite scarce data in nonagenarians, many series confirm that radiation therapy is well tolerated in the elderly. Besides, clinical trials show that RT after BCS compared

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with BCS alone reduces breast cancer recurrence among older women with early-stage disease. It could seem therefore reasonable to refer to RT only patients with life expectancy greater than 5 years and a poor prognosis tumor (large tumors, positive lymph nodes, or negative hormone receptors) [12]. The standard fractionation for curative adjuvant RT following primary surgery for early breast cancer classically delivers a dose of 50 Gy in 25 daily fractions (\pm boost) over 5 weeks. However, very old patients with poor performance status tolerate hardly such treatment without deterioration of their quality of life. Hypofractionated regimens are frequently used, to minimize the burden of a relatively protracted treatment. Randomized trials indicate that a lower total dose delivered in fewer, larger fractions is as safe and effective. However, to our knowledge, no randomized study has specifically assessed the role of hypofractionated regimens in the management of elderly breast cancer patients [13,14]. In order to provide broader clinical data about effectiveness, delivery modalities and safety of radiation therapy in nonagenarians with breast cancer, we report on our experience of 44 patients aged 90 years or older with breast cancer in five different French centers.

Materials and methods

Patients and tumors

Records from RT departments from two university hospitals and from two private centers were reviewed to identify patients who underwent RT for breast cancer over past decade and who were aged 90 years or older. Patients' characteristics (age, gender, living place, general health status) were examined, as well as tumor stage. As none of the centers involved in this study had oncogeriatric resource at this time, patients did not receive routinely an integrated oncogeriatric assessment before beginning therapy.

Treatment characteristics

Treatment intents were classified as potentially curative or palliative, according to the judgment of physician at time of therapeutic decision. The following treatment characteristics were examined: total dose, treatment duration, fractionation, and the use of concomitant radiosensitizers.

Data analysis

Toxicity was assessed weekly during the RT course using CTCAE v3.0 criteria (National Cancer Institute Common Toxicity Criteria), then at regular intervals until last follow-up. All patients were analyzed for acute toxicity, whatever follow up time. Late toxicity was any toxicity occurring more than 6 months after completion of RT. Only patients with at least three weeks follow-up were analyzed for effectiveness and survival. Effectiveness was defined according to the treatment intend. In curative intent, we examined local control at last follow up. In palliative intent, we analyzed control of symptoms.

Results

Patients

From 2003 to 2013, 44 female patients aged 90 years or older receiving breast or chest RT for a breast malignant tumor were identified, in five French institutions (two university hospitals, two private centers, one general public hospital). These patients accounted for 0.2–0.5% (depending on the institution) of all breast cancer patients receiving RT during this time interval. Although this

is a roughly estimate due to the lack of exhaustive cancer registry in our institutions in the earlier years of this time interval, about 15% of breast cancer patients with localized tumor were referred to a radiotherapist. Mean age was 92 years. Twenty-one patients (48%) had a general health status altered (PS 2–3) at the beginning of RT, according to the World Health Organization classification. Most patients were living at home. Patients' characteristics at time of RT course are given in Table 1.

Tumors and previous therapies

Histologically, most frequent breast tumors were invasive ductal carcinoma (82%), followed with invasive lobular carcinoma (6.8%), sarcoma (2.3%) and mucinous carcinoma (2.3%). Three patients (6.8%) had an invasive carcinoma without further details. Most patients (37%) presented with locally advanced (IIIB) disease. The SBR grade was mainly 2 and 3 for half of the patients. Most tumors expressed estrogen receptor (77%) or progesterone receptor (61.4%). Human epidermal growth factor receptor 2 (HER2) was expressed in only two tumors (4.5%). At time of RT, 39 patients

Table 1
Characteristics of patients and tumors.

	n	(%)
<i>Patients' characteristics</i>		
Number	44	(100)
Mean age (SD)	92 [89.1–97.8]	
Gender		
Female	44	(100)
PS		
0–1	23	(52)
2–3	21	(48)
Living place		
Home	28	(64)
Institution	10	(23)
Unknown	6	(13.6)
<i>Tumors' characteristics</i>		
<i>Histology</i>		
Invasive ductal carcinoma	36	(82)
Invasive lobular carcinoma	3	(7)
Invasive carcinoma	3	(7)
Sarcoma	1	(2)
Mucinous carcinoma	1	(2)
<i>Stage</i>		
I	4	(9)
IIA	9	(20)
IIB	8	(18)
IIIA	5	(11.4)
IIIB	16	(37)
IIIC	0	(0)
IV	1	(2)
No staging	1	(2)
<i>SBR grade</i>		
SBR 1	3	(7)
SBR 2	19	(43)
SBR3	16	(37)
Unknown	6	(14)
<i>ER status</i>		
Positive	34	(77)
Negative	9	(20)
Unknown	1	(2.3)
<i>PR status</i>		
Positive	27	(61)
Negative	16	(36)
Unknown	1	(2.3)
<i>HER2 status</i>		
Positive	2	(5)
Negative	41	(93)
Unknown	1	(2)

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; PS: performance status; PR: progesterone receptor; SBR: Scarf Bloom and Richardson; SD: standard deviation.

(88%) had previously received one or more anticancer treatment(s). Those include surgery of primary tumor in 26 patients (59%) and hormone manipulation in 13 patients (30%). Characteristics of tumors and previously delivered therapies are presented in Table 1.

Treatment intent

A total of 44 RT courses were delivered, including 32 treatments (73%) with curative intent and 12 treatments (27%) with palliative intent. At multivariate analysis, the performance status ($p = 0.018$) and stage ($p < 0.01$) were significantly associated with a curative intent RT.

Treatment characteristics

All treatments were delivered using high megavoltage linear accelerators and conformal dosimetry. Median total prescribed dose was 40 Gy (23–66 Gy). Most patients (77%) received hypofractionated RT (HFRT). Dose per fraction was above 2.5 Gy. 8 radiation courses (18%) were normofractionated. Median number of delivered fractions was 10 (4–33 fractions). Breast (75%), lymph nodes (4%) or both (20%) were the irradiated zones.

Concurrent hormone therapy was delivered in only 4 patients and no patient received concurrent chemotherapy. Split course was used in one patient. Treatment characteristics are presented in Table 2.

Effectiveness

Thirteen patients had a follow-up less than three weeks after completion of radiotherapy and were not analyzed for effectiveness. However, all of them were alive with disease controlled before being lost to follow-up. In the 31 remaining patients (curative intent: 26 patients; palliative intent: 5 patients), median and mean follow-up times were 39 weeks and 61 weeks (ranging from three weeks to 5.4 years). At last follow-up, 23 patients (74%) had their disease controlled until last follow-up: 17 patients (55%) experienced complete response, 6 patients (19%) experienced partial response including three stable disease, and two patients (6%) experienced tumor progression, including local progression. Tumor control was unspecified in 6 patients (19%). Data are presented in Table 3.

Table 2
Radiotherapy parameters.

Treatment intent and Target volumes	n	(%)
Treatment intent		
Palliative	12	(27)
Curative	32	(73)
Target volumes		
Primary Site (breast)	33	(75)
Lymph nodes	2	(5)
Primary Site and Lymph nodes 1	9	(20)
Dose, Fractions and treatment duration	Median	(min–max)
Dose		
Total mean dose (Gy)	40.5	(23–66)
Fractions		
Number of fractions	10	(4–33)
Dose per fraction (Gy)		
<2Gy	8 patients	(18)
>2.5Gy	34 patients	(77)
Total Treatment duration (days)	31,5	[13–52]
Concomitant treatment		
Hormone Therapy	4	(9)
Surgery	0	

Gy: Grays; max: maximum.

Table 3
Follow-up and tumor control in patients analyzable for effectiveness.

	n	(%)
Follow-up		
Number of patients	31	
Median follow-up time	39 weeks	
Mean follow-up time	61 weeks	
Range of follow-up time	3 weeks–5.4 years	
Status at last follow-up		
Alive	27	(88)
Deceased	4	(29)
Causes of death		
Cancer	2	(6)
Other	2	(6)
Not intended treatment disruption		
For toxicity	1	(2)
For patient's noncompliance	0	(0)
Tumor control at last follow-up		
Controlled	23	(74)
Complete response	17	(55)
Partial response	6	(20)
Including stable disease	3	(10)
Tumor relapse or progression	2	(6)
None reported	6	(20)

min: minimum; max: maximum.

Toxicity

All patients were analyzed for acute toxicity. There was no acute toxicity in 18 patients (41%). Maximal acute toxicity was grade 3 in 1 patient (2%). Fifteen patients (34%) had a grade 1 toxicity and ten patients (22%) had a grade 2 toxicity. RT could not be completed in one patient (2%) because of skin toxicity.

Sixteen patients (36%) had a follow-up exceeding 6 months and were thus assessable for long-term toxicity. No delayed toxicity was reported in 40 patients (90.9%). Grade 1–2 delayed toxicity was reported in four patients (9%). No patient experienced grade 3 or more toxicity.

Toxicity data are detailed in Table 4.

Discussion

The number of nonagenarians seeking treatment for breast cancer is increasing. Although several series reviewed the treatment of patients in their eighties, these reports contain very few patients in their nineties [15–20]. In 1996, Ballard-Barbash et al. had examined data from the Surveillance, Epidemiology, and End Results (SEER) Program and found that breast cancer patients aged 80 years and older were much less likely to receive postoperative RT [21]. The CALGB 9343 study investigated whether there was a benefit to adjuvant RT after breast conservative surgery and tamoxifen in women age ≥ 70 years with early-stage breast cancer. With median follow-up of 12.6 years, authors found that there was

Table 4
Toxicity data.

Criteria	n	(%)
Acute Toxicity (CTCAE v3)		
Grade 0	18	(41)
Grade 1	15	(34)
Grade 2	10	(23)
Grade 3	1	(2)
Grade 4	0	(0)
Late Toxicity (CTCAE v3)		
Grade 0	40	(91)
Grade 1	3	(7)
Grade 2	1	(2)

CTCAE v3: Common Terminology Criteria for Adverse Events v3.0.

a small improvement in locoregional recurrence rates with the addition of RT, which did not translate into an advantage in survival [22].

As there was no exhaustive registrar for breast cancer patients treated in our institutions during this time interval, we could not determine how many breast cancer patients were not referred for RT. A study analyzed symptomatic and screen detected breast cancers diagnosed in 2006 in the United Kingdom. About 15% of breast cancer patients diagnosed over 90 years of age had received conservative or radical surgery. Radiotherapy was delivered in less than 20% of breast cancer patients, showing that RT is underused in these elderly patients [23]. This is consistent with our estimate that about 85% of breast cancer patients aged more than 90 years did not receive RT of their primary breast disease.

Breast cancer characteristics (tumor grade, histology, hormone receptivity) appeared similar between women age >90 years and younger women [24]. Only 59% of patients had received surgery of primary tumor, which is the mainstay of treatment for localized breast cancers [4]. This illustrates the view that older patients are less likely to be fit for surgery [25]. The incidence of co-morbidity in older patients is also greater, which may potentially increase the risks of general anesthetic. Hamaker et al. have shown that omission of surgery increased significantly over 80 years and older. Instead, patients frequently received hormone therapy as an alternative to surgery [26].

Older patients are under-represented in trials of adjuvant radiotherapy [27]. The SEER program has evidenced a decline in the use of radiotherapy with age, irrespective of co-morbidity, from 78% of fit 65–69 years old to just 28% of women aged over 80 [28]. Older patients are more likely to need assistance for travelling to the radiotherapy unit every day for the course of their treatment. This issue justifies the interest of hypofractionated therapy, which allows a good local control with acceptable toxicity. Besides, hypofractionated RT associated with hormonal therapy is a good alternative to surgery in non-operable old patients and in case of patient refusal to surgery and to standard fractionation [29–31].

Our study did not allow drawing definitive conclusions regarding the impact of RT on local control, progression-free survival, survival, or even quality of life in patients aged 90 years and more. Only an adequate study of deliberate undertreatment and monitoring the recurrence rate will answer this issue. Radiation therapy was safely administered with both curative and palliative intent with the completion in more than 80% of patients. This suggests that nonagenarians with few comorbidities and a good performance status could be treated for their breast cancer, provided that RT plans are tailored with particular attention paid to performance status and goals of care. However, Dellapasqua et al. have highlighted that the choice of adjuvant therapy for an elderly patient in clinical practice is currently driven by age itself as well as stereotypical attitudes of oncologists, rather than an objective evaluation of predictive and prognostic factors and geriatric parameters [32].

This study also shows that assessment of geriatric vulnerabilities remains still insufficiently developed in clinical routine. An accurate assessment of frailty, whether with a time consuming CGA or with an equally effective quick screening test (e.g. TUG, VES-13) should be mandatory in clinical practice, research and series reporting. It is also mandatory to clearly identify therapeutic objectives and to redefine the true benefit of delivering adjuvant RT to nonagenarians who had an early screened and adequately excised breast cancer. Only a therapeutic trial will answer this question, may be through the inclusion of fit nonagenarians with breast cancer in prospective clinical trials.

Ethics approval

No approval was required.

Conflict of interest statement

No authors have conflict of interests.

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