

Radiation Therapy in the Elderly with Early Stage Breast Cancer: Review and Role of New Technology

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Abstract

In 2013, breast cancer affected 232,340 women in the US. Of these diagnoses, 52% were in women aged 65 and older. Although age is a risk factor for the development of breast cancer, women diagnosed at an older age generally have a more favorable prognosis due to often less aggressive tumor biology. Elderly women tend to have higher rates of hormone receptor positive tumors and also tumors with lower proliferative indices (Ki-67). Despite these favorable prognostic factors, breast cancer specific mortality has only decreased at a rate of 1.1% per year for women aged 75+ in comparison to 2.4% per year for women aged <50. It has been hypothesized that this is related to under-treatment of elderly patients due to increased comorbidities which can limit treatment options as well as social influences such as distance to treatment facilities and lack of transportation. Older women are less likely to be offered standard treatment including surgery, radiotherapy, chemotherapy and endocrine therapy regardless of their breast cancer stage.

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benefit of treatment to a woman over the age of 70 is trying to estimate each individual patient's life expectancy.

Introduction

In 2013, breast cancer affected 232,340 women in the US. Of these diagnoses, 52% were in women aged 65 and older [1]. Although age is a risk factor for the development of breast cancer, women diagnosed at an older age generally have a more favorable prognosis due to often less aggressive tumor biology. Elderly women tend to have higher rates of hormone receptor positive tumors and also tumors with lower proliferative indices (Ki-67). Despite these favorable prognostic factors, breast cancer specific mortality has only decreased at a rate of 1.1% per year for women aged 75+ in comparison to 2.4% per year for women aged <50 [2]. It has been hypothesized that this is related to under-treatment of elderly patients due to increased comorbidities which can limit treatment options as well as social influences such as distance to treatment facilities and lack of transportation [3-5]. Older women are less likely to be offered standard treatment including surgery, radiotherapy, chemotherapy and endocrine therapy regardless of their breast cancer stage [6].

Standard treatment of early stage breast cancer includes mastectomy versus breast conserving therapy consisting of breast conserving surgery (BCS), and radiation therapy (RT). Hormonal therapy is offered to women with estrogen receptor positive disease and chemotherapy is given adjuvantly based on the risk of distant metastases which can be estimated by tumor size, histologic grade, lymph node involvement and more recently by the use of risk predictive tools such as Oncotype DX® or Mammprint.

Various tools have been created to help determine the risk of mastectomy free survival in the elderly population including the following tool available through MDACC: www.mdanderson.org/RadiationBenefitPredictor [7]. The greatest difficulty in estimating the

Limitations of Treatment in the Elderly

In elderly patients, the optimal surgery is sometimes impacted by co-morbidities. Mastectomy requires general anesthesia, is a longer procedure, has an increased risk of morbidity, decreased cosmetic outcomes, and for select patients, additional reconstructive procedures, as many elderly women continue to desire breast symmetry. As such, elderly women may still undergo the placement of an implant or various other plastic surgery procedures to provide symmetry. Lumpectomy is usually performed under general anesthesia but can be done under local anesthesia for patients at high risk. Improved cosmetic outcome is the clear advantage to lumpectomy over mastectomy with only a small minority of patients needing an additional procedure for maintenance of breast symmetry. Thus, BCS is often elected for many women.

Lymph node assessment with a sentinel lymph node procedure is sometimes omitted for three reasons. First, patients at high risk for surgical complications should not undergo general anesthesia. Second, if a patient is deemed not to be a chemotherapy candidate due to medical comorbidities, then lymph node assessment is not performed as the additional information would not impact systemic therapy decisions. The third rationale for omitting lymph node assessment is based on extrapolation from ACOSOG Z0011 which demonstrated the lack of benefit of an axillary dissection in a clinically uninvolved axilla [8]. Please note that even though sentinel lymph node involvement does not impact the use of chemotherapy or the use of an axillary dissection, there is growing evidence that the radiation target (i.e. inclusion of the surrounding regional lymph nodes) can significantly impact breast related mortality.

Use of hormonal therapy is also sometimes limited in elderly patients due to comorbidities, specifically a history of blood clots or

stroke. In several studies, elderly patients have been shown to be less compliant with hormone therapy even with the use of newer aromatase inhibitors [9,10]. Chemotherapy is often difficult to administer in the elderly population due to co-morbid conditions, specifically cardiac function.

Radiation therapy can sometimes be difficult to administer to the elderly population. Typically breast cancer patients lie in the supine position with the ipsilateral or bilateral arms above the head. A variety of immobilization devices can be used including a breast board or arm shuttle. The supine position can be difficult for many patients with ipsilateral shoulder mobility issues or back problems which tend to increase with increasing age. The other common position for treatment is for patients to lie in the prone position, which can be more difficult for some elderly patients. Transportation problems represent another rate limiting steps for many elderly patients since RT is a daily treatment that can last several weeks. Many elderly patients don't drive or only drive within certain areas. If the closest radiation facility is over 25 miles away, the ability to receive radiation therapy is severely limited which can result in increased local recurrences, unnecessary mastectomies and a decrease in breast cancer related mortality [11].

Data on the Impact of RT in the Elderly

Post-operative whole breast irradiation is the standard of care in all patients undergoing breast conserving therapy. In the Oxford meta-analysis trials comparing BCS for early stage breast cancer with or without whole breast radiation therapy, the addition of whole breast RT resulted in a 2x reduction in first relapse. However, the absolute reduction at 10 years in women 70+ is only 8.8% compared to women <70 at 17.7. Breast radiation therapy has also been shown to improve overall survival and decrease the risk of distant metastases [12,13].

At least two large phase III randomized trials have been performed in elderly patients evaluating the benefit of LPC+ hormonal therapy with or without whole breast RT. The CALGB 9343 study randomized over 600 women aged 70+ and was designed to determine whether radiotherapy would reduce the risk of local recurrence. With a median follow up of 12.6 years, this trial demonstrated that the addition of whole breast RT resulted in a significant decrease in the risk of ipsilateral breast tumor recurrence from 7% at 10 years to 2% [14]. There was no difference in overall survival between the 2 groups, but the study was not powered to answer this question. The Princess Margaret Hospital performed a similar study in 769 women aged 50+ (median age 68) with stage I/II, node negative breast cancers. The randomization was BCS+ hormonal therapy with or without whole breast RT. The combination of RT and tamoxifen reduced the 8 year local recurrence rates from 12.2% to 4.1% and improved DFS from 76% to 82% [15]. Due to the lack of overall survival benefit, many investigators suggest omission of whole breast radiotherapy in this age group [14,16].

One of the limitations of these studies is that they did not sub-stratify patients based on known prognostic factors for recurrence such as tumor grade, LVI and margin status (close versus widely negative). Additionally, these analyses do not discuss the compliance of hormonal therapy use which, as previously discussed, is a known issue in the elderly. If indeed patients on these studies were compliant with 5 years of tamoxifen use, then the local recurrence rates are likely lower than what would be seen in the general population. Lastly, an improvement in overall survival with the addition of radiation therapy

to breast conserving surgery has only been shown in a large meta-analysis including 7300 women [17]. Thus, it seems unreasonable to use a lack of survival benefit in two smaller studies with combined total of 1369 patients as the rationale to not give whole breast radiation therapy.

At least two SEER Database studies have evaluated the utilization and potential benefit of WBI in the elderly population. Cohen et al demonstrated that the use of RT decreased with patient age with 80% of women between ages 70-74; 74% between ages 75-79 and 61% between ages 80-84. In addition and probably more importantly, these same investigators demonstrated an improvement in overall survival as well as breast cancer specific survival in women aged 70+ with the addition of RT to LPC [11]. Median survival was 13.1 years for women treated with surgery and RT but only 11.1 years for those treated with surgery alone (Figure 1). Breast cancer specific survival was improved by approximately 2% and this improvement persisted at 15 years. Overall survival was improved by 15.5% at 5 years (88.6 vs 73.1); 23.3% at 10 years (65 vs 41.7%) and 19.6% at 15 years (39.6 vs 20%). Korah et al. performed a similar study demonstrating improved cancer specific survival and overall survival with the addition of radiation to surgery in patients with stage T1/2, node negative, ER+ breast cancers [18]. They showed a similar absolute improvement of about 2% in breast cancer specific survival at 5 years which doubled to 4% at 8 years. Overall survival also favored the addition of RT with an absolute improvement of 19% at 5 years and 23% at 10 years.

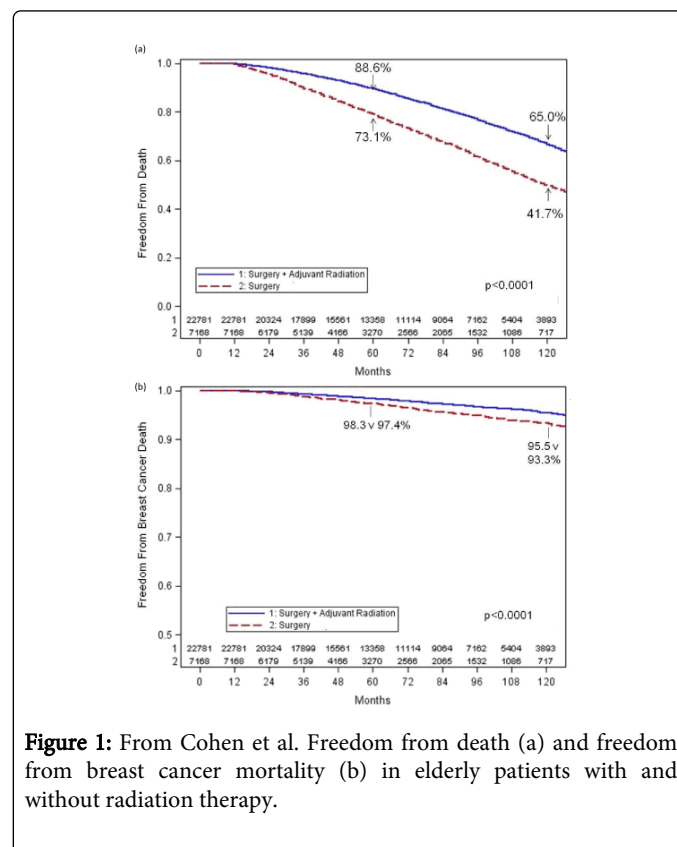


Figure 1: From Cohen et al. Freedom from death (a) and freedom from breast cancer mortality (b) in elderly patients with and without radiation therapy.

The International Society of Geriatric Oncology recently published radiotherapy recommendations for various cancer sites, including breast cancer [19]. In their recommendations for early stage breast cancer they conclude that all 'fit' elderly women should still be offered and recommended radiation therapy (Table 1).

Fit older patients are candidates for WBI after breast conserving surgery for invasive cancer and for higher-risk DCIS
Whole Breast Irradiation (WBI) with a boost to the site of excision is appropriate for all older patients with invasive breast cancer; there is no specific subgroup from whom WBI can be systematically omitted.
Patients >50 are candidates for a hypofractionated schedule when lymph node irradiation is not indicated
Partial breast irradiation should still be considered investigational
3D based planning is advised to minimize lung/heart doses

Table 1: International Society of Geriatric Oncology (SIOG) recommendations for breast cancer radiation in the elderly.

Thus, instead of asking whether these patients should undergo RT, we should be asking how can we make treatment more readily available, more accessible and less time consuming. Below are several different techniques/schedules of radiation therapy that can and should be considered for the elderly population.

Hypofractionation

One option for whole breast RT in the elderly is to shorten the overall course of treatment. Multiple randomized studies have been performed utilizing this approach and show equivalent local recurrence rates, cosmetic outcomes and toxicities [20-22]. A possible exception is in patients with high grade tumors who may have a slightly increased local recurrence risk. The most common hypofractionation schedule utilized in the United States has been the “Canadian regimen” which is 16 fractions 2.66Gy for a total whole breast RT dose of 42.56 Gy. This regimen does not include a boost. To include a boost, several investigators have developed shortened regimens utilizing intensity modulation with an integrated boost to the tumor bed [23,24]. These trials led to the experimental arm that was used in the recently completed RTOG protocol (10-05) (Available at www.rtog.org). Hypofractionation is only utilized if the regional lymphatics are not being treated.

One of the limitations of using hypofractionated RT is the patient’s body habitus/size. If the patient’s separation is greater than 25 cm as measured on CT scan drawing a straight line from the sternum to the mid axilla on the affected side, then she may not be a candidate for this approach due to ‘hot spots’ in the breast which could adversely affect cosmesis and quality of life related to fibrosis. Using modern techniques of radiation therapy such as prone positioning or Intensity Modulated Radiation Therapy (IMRT), ‘hot spots’ can carefully be avoided in the majority of patients even with these separations. Another concern expressed by some is dose to the heart in left-sided patients, as it is generally known at the biological level that larger RT doses can result in increased risk of late normal tissue side effects. It would be debatable how relevant this concern is in the elderly.

The recently published American Society of Radiation Oncology (ASTRO) “Choosing Wisely Guidelines” recommends that a hypofractionated regimen be offered and recommended to all patients undergoing breast conserving therapy [25]. Despite this recommendation there continues to be some resistance to this approach in the younger population, especially those with high grade tumors. Hypofractionation significantly shortens the overall course of radiation therapy from 5-7 weeks to around 3 weeks, however, treatment length and transportation can still be problematic for the elderly. Further shortening of whole breast radiotherapy to one week is under investigation [26].

Accelerated Partial Breast Irradiation (APBI)

Another option that may be particularly suited to the elderly is APBI. APBI is a technique where treatment is delivered to the LPC bed alone along with a margin of normal breast tissue. The rationale for this approach is based on the observation that the LPC bed is the area at highest risk of recurrence. APBI is delivered twice daily for 5 consecutive days with treatments delivered at least 6 hours apart.

Large phase III data regarding the outcomes of APBI have been completed but long term results have yet to be reported. The results of long term single arm institutional and multi-institutional results are available. Generally, these results indicate similar recurrence rates in the ipsilateral breast for well selected patients.

Various guidelines exist to help determine which patients are appropriate candidates for an APBI approach including the ASTRO consensus guidelines the American Society of Breast Surgeon’s guidelines and the American Brachytherapy Society Guidelines [27-29]. In all of these guidelines, age is an important factor, with elderly patients being considered most suitable for this approach (Table 2). The ASTRO consensus statement indicates that suitable patients have the following factors: age >60; T1, pN0, ER+, no LVI, negative margins (defined by >2 mm), unicentric/unifocal disease and no EIC. Fortunately, these criteria are met by a large majority of elderly patients.

Group	Age	Histology	Tumor size	Hormone receptor status	Margin status	LN status
ASTRO	>= 60	Invasive ductal or other favorable histologies	</= 2 cm	ER+	Negative (at least 2 mm)	pN0 (i-,i+)
American Society of Breast Surgeons	>= 45	IDC or DCIS	</= 3 cm	NS	Margin negative	pN0

American Brachytherapy Society Task Group	>= 50	IDC	<= 3 cm	NS	NS	NO
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Table 2: Guidelines for appropriate/suitable patients for APBI. IDC=Invasive Ductal Carcinoma; DCIS =Ductal Carcinoma in situ; NS=Not Specified; ER=Estrogen Receptor Positive.

The techniques available for APBI include interstitial brachytherapy, intracavitary or balloon brachytherapy and external beam APBI. The risks, benefits and potential side effects of each therapy are slightly different. Additionally, some of these techniques require additional procedures and technology, thus all are not widely available. Additionally, some techniques are not available depending on the size and location of the lumpectomy cavity. The most popular choice in the US by far (>70% of the accrual) is external beam APBI due to its non-invasive nature and the fact that it does not require any additional procedures. Unfortunately, there is growing concern that this approach has higher side effects in comparison to whole breast radiation. The Canadian RAPID study randomized patients to whole breast irradiation using a hypofractionated approach of 42.5Gy in 16 fractions or 50Gy in 25 fractions +/- boost versus external beam APBI of 38.5Gy in 10 fractions, twice daily. Early results indicate that the APBI arm had worse cosmesis at 3 years compared to the whole breast irradiation (WBI) group as assessed by trained nurses (29 vs 17%, p<0.001), patients (26 vs 18%, p=0.0022) and physicians reviewing digital photographs (35 vs 17%, p<0.001). Additionally grade 1 and 2 toxicities were increased in the APBI group compared to the WBI but there was no difference in grade 3+ toxicities [30]. To date, no specific studies of APBI have been performed on the elderly population even though this cohort of patients has been considered to be the ‘most suitable’ for this approach.

Intra-Operative Radiation Therapy (IORT)

IORT is a technique where by radiation therapy is delivered in one session at the time of surgery immediately following the lumpectomy and sentinel lymph node procedure. This technique requires additional technology including a lead shielded operating room, the ability for the anesthesiologist to step out of the operating room while the patient is receiving the treatment, and additional time under anesthesia for treatment set up, treatment planning and treatment delivery. If the patient is subsequently found to have unanticipated pathological findings, whole breast irradiation can be delivered post-operatively.

Two large randomized studies have compared WBI to IORT. The TARGIT trial evaluated over 2000 patients using an intraoperative dose of 20 Gy [31]. The local recurrence rates were 3.3% in the IORT group and 1.3% in the WBI group with no difference in reported toxicities. This trial included women of all ages. The ELIOT trial randomized over 1300 patients up to the age of 75 with up to 2.5 cm tumors to WBI versus single fraction IORT of 21Gy [32]. The ipsilateral breast tumor recurrence rate was 4.4% in the IORT group and 0.4% in the WBI. These higher local failure rates with IORT are likely related to inadequate target coverage of subclinical disease [33].

Long term follow up with IORT is currently lacking as the longest follow up is a median of 5.8 years. However, through various statistical analyses, IORT results are thought to be equivalent and proponents of this technique are eager to push it forward. To date, no specific studies have been performed in the elderly population.

GammaPod™ Stereotactic Breast Radiotherapy and other Ablative Therapies

The GammaPod is a novel breast stereotactic radiosurgery device developed and created at the University of Maryland. This procedure includes a breast immobilization device that utilizes a vacuum-type technology, a dynamic treatment couch, and 36 rotating Cobalt-60 sources, which create dose distributions to a lumpectomy cavity or breast tumor that are substantially better than any currently available external beam radiotherapy device. Patients are treated in the prone position with the immobilization device in place. The GammaPod has the ability to treat patients in the post-operative setting, but can also be used to treat patients pre-operatively. This allows immediate treatment similar to IORT but with the benefit of more accurate target volume [33] and a non-invasive approach. GammaPod also offers substantial dosimetric advantages in to other devices which allows escalation of radiation dose, possibly to “ablative” doses. The GammaPod could lead to a paradigm shift in the management of early breast cancer patients. We are already seeing the success of this in patients with early stage non-small cell lung cancers [34], in similar technology has led to >90% control rates in small tumors. The GammaPod technology would be ideal for the elderly population due to its non-invasive nature and its ability to deliver treatment in as few as one setting. If the GammaPod were to be as successful as SBRT in the lung, it may have the potential to challenge the paradigm of surgery in select patients with early stage breast cancers.

Conclusion

Data continue to show the clear benefit of post-operative radiotherapy for elderly patients with early breast cancer. Post-operative radiotherapy improves local control, and in some studies, cancer specific survival and overall survival. Compliance with hormonal therapy is suboptimal in the elderly. Radiation therapy should be recommended for all elderly patients who are able to tolerate treatment and do not have a comorbidity associated with an imminent threat to life. Rather than focusing on whether or not to give radiation therapy, we must focus on how best to deliver radiation therapy. With the increasing number of elderly patients, research must specifically focus on the needs of this population.

Recommendations (Figure 2)

1. All elderly patients with a reasonable life expectancy should be considered for adjuvant radiotherapy (i.e. those with no life-threatening comorbidities).
2. Hypofractionated regimens should be considered first unless contraindicated such as when nodal chains are included.
3. Partial breast irradiation techniques can be considered secondarily in select patients who are deemed ‘suitable’ based upon published guidelines. This may be due to patient transportation issues or availability of partial breast irradiation techniques. PBI should not be considered as the primary modality due to lack of specific studies targeting this patient

population as well as continued concerns regarding patient cosmetic outcomes.

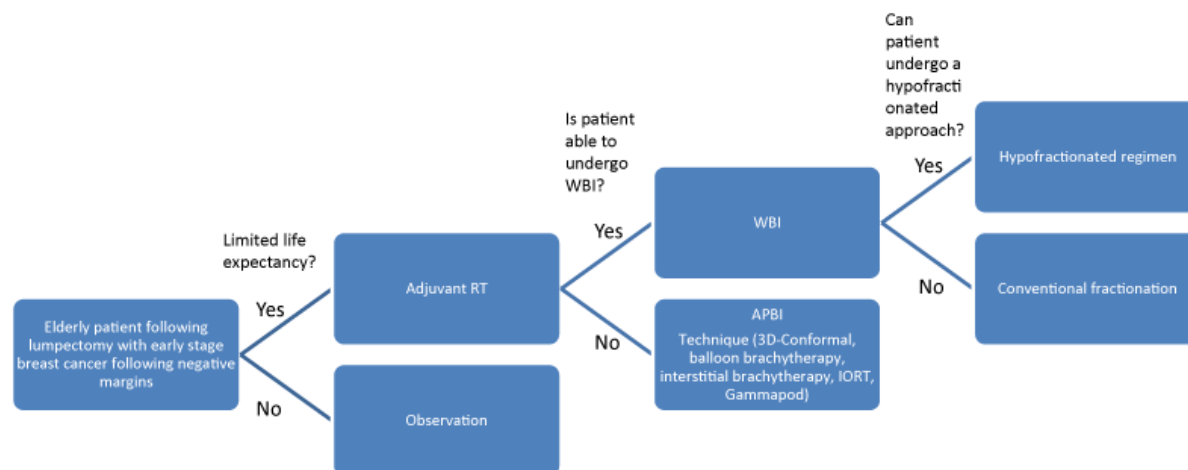


Figure 2: Radiation therapy approach to elderly patient with early stage breast cancer.

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