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De-escalation of surgical and radiation treatment in elderly luminal breast cancer patients, single institution report and review of the evidence

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Abstract

Background De-intensification of anti-cancer therapy without significantly affecting outcomes is an important goal. Omission of axillary surgery or breast radiation is considered a reasonable option in elderly patients with early-stage breast cancer and good prognostic factors. Data on avoidance of both axillary surgery and radiation therapy (RT) is scarce and inconclusive.

Methods A retrospective cohort study comprising all women aged 70 years and older diagnosed with early, hormone receptor (HR) positive, HER2-negative breast cancer treated with breast-conserving surgery (BCS) without sentinel lymph node biopsy (SLNB) and RT in a large tertiary center (between 2016 and 2021). Data on patient and tumor characteristics as well as outcomes including local recurrence, loco-regional recurrence, distant metastases, and death were extracted. Disease free survival (DFS) was assessed by Kaplan-Meier analysis. The Cox proportional hazard regression model was performed to identify factors (demographic and clinical characteristics of the patients) that predict the disease recurrence or death.

Results A total of 100 women were included, median age of patients was 81. All patients had clinically node-negative disease with a median tumor size was 13 mm. Five (5%) women had lymphovascular invasion. At a median follow-up of 3.9 years, there were 7 (7%) recurrences, 4 local, 2 local-regional, and one distant. The median DFS for the entire group was 42 months (11–128). Eight patients (8%) died, 5 of them for reasons unrelated to breast cancer (3 of unknown reason). Tumor size larger than 13 mm was associated with significantly worse DFS (HR = 4.02, 95% CI 1.08–14.99, $p = 0.04$).

Conclusion Omission of both SLNB and adjuvant RT is feasible in elderly, early breast cancer patients with small luminal tumors.

Keywords Breast, Radiation, Omission, Sentinel lymph node biopsy

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Introduction

The standard treatment of early-stage (T1-2, node-negative), hormone receptor (HR) positive, HER2-negative breast cancer usually consists of local therapy to the breast (either lumpectomy or mastectomy), sentinel lymph node biopsy (SLNB), and systemic endocrine treatment. Adjuvant radiation therapy (RT) is usually recommended after lumpectomy.

RT after breast-conserving surgery decreases the risk of ipsilateral breast cancer recurrence and improves breast cancer mortality [1]. The omission of adjuvant radiation treatment in elderly patients diagnosed with early-stage breast cancer with favorable prognostic features has been a subject of investigation for more than two decades. Several well-designed studies have shown that RT is associated with improvement in local recurrence (absolute risk reduction of 5–8% in 10 years), but with no difference in overall survival (OS) [2–4]. Several international guidelines permit the omission of RT in carefully selected patients (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) [5].

The Society of Surgical Oncology (SSO) recommended in 2016 to avoid the routine use of sentinel node biopsy in clinically node-negative greater than 70-year-old women with early-stage HR-positive, HER2-negative invasive breast cancer [6]. This statement was primarily based on studies demonstrating no difference in breast cancer mortality with or without axillary dissection [3, 7]. The axillary recurrence rate on the omission of lymph node dissection in this category of patients is low. The potential morbidity of axillary surgery in elderly patients who often suffer from severe co-morbidities must be considered [8, 9].

Avoidance of both axillary surgery and adjuvant RT in elderly early-stage, node-negative, HR-positive, HER2-negative breast cancer patients has been scarcely reported in the literature. We herein report the results of our retrospective study of the omission of SLNB and RT in elderly patients with early-stage, favorable pathological prognostic features breast cancer treated in a large tertiary center.

Methods

We reviewed all 393 medical records of female patients aged 70 years and above who underwent lumpectomy at Ichilov Medical Center between 2016 and 2021. From this cohort, we identified every woman (100 total) diagnosed with clinical T1N0, HR-positive, HER2-negative breast cancer who underwent breast-conserving surgery (BCS) without SLNB and RT. Other patients, including those who underwent SLNB, had DCIS, benign lesions, received RT or had other breast cancer subtypes, were excluded from the study. The decision to avoid SLNB

and adjuvant RT was restricted to patients with tumors measuring less than 20 mm, as per institutional policy. This decision was made after a multidisciplinary breast cancer tumor board reviewed the clinical characteristics, pathology reports, and imaging findings. All patients were recommended to receive adjuvant hormonal therapy according to current guidelines. Demographics, patient and tumor characteristics, and outcome of treatment were extracted from the hospital's electronic medical charts. They included the patient's age, tumor size, histology, grade, lymphovascular invasion (LVI) presence, tumor margins status (no tumor on ink defined negative margins), estrogen and progesterone receptors, HER2 expression, Ki67 proliferation index, and receipt of adjuvant endocrine and radiation treatment. Local recurrence (LR) was defined as recurrence in the breast itself, local-regional recurrence (LRR) was defined as recurrence in the breast and axillary or supraclavicular nodes, disease free survival (DFS) was defined as time from date of diagnosis to any recurrence (local, local-regional or distant) or death. As data were analyzed anonymously, no consent was required. The study protocol was approved by our institutional ethics committee.

Statistical analysis

All independent variables were characterized by appropriate descriptive measures. We tested the statistical independence of each variable (factor) with the Status using Chi-Squared and Fisher-Exact tests. DFS was estimated by the Kaplan-Meier method for the whole population. It was also calculated for low and high variable values, and the difference was tested for significance. The Cox proportional hazard regression model was performed to identify factors (demographic and clinical characteristics of the patients) that predict the disease recurrence or death. For statistical analyses, we used SPSS 29 software.

Results

The median age of patients was 81 (range 73–95). All patients had lumpectomy of the primary tumor without SLNB and were clinically node-negative. The median tumor size was 13 mm (2–32). The mean distance of the tumor to the inked surgical margins was 4.5 mm. In 97% of cases, the surgical margins were negative. One of the three patients with positive margins underwent re-excision (the other two were reluctant to have another procedure). Most of the patients (99%) were hormone receptor-positive (patients and tumor characteristics are shown in Table 1). Eighty patients (80%) received endocrine treatment for 5 years.

At a median follow-up of 3.9 years local, local-regional and distant metastases developed in 4, 2, and 1 patients,

Table 1 Patient characteristics

Total number	100
Age (years), median	81 (73–95, IQR 7)
Histology (%)	
IDC	69
ILC	13
Mucinous	15
Mixed	3
Tumor size (mm), median	13 (2–32, IQR 8)
cN0	100%
Hormone Receptor status	99% positive 1% negative
Margin*	3% positive 97% negative
Lymphovascular invasion **	95% negative 5% positive
Systemic endocrine treatment	20% no 80% yes
KI 67 (%), mean ***	10 (1–60, IQR 7)
Luminal A (KI67 < 15%)	79%
Luminal B	21%

*3 positive margins

**9 missing

***22missing

respectively. Notably, in all cases of recurrence, the pathology after the initial surgery showed negative margins and no lymphovascular invasion (LVI). Additionally, in most recurrence cases (86%), the patients have received some form of endocrine therapy before the event. Upon local recurrence 1 patient underwent a mastectomy, one lumpectomy, and adjuvant RT and 2 patients received only endocrine treatment without further surgery or RT. One patient with nodal metastases had a mastectomy with adjuvant RT to the chest wall and regional lymphatics and another lumpectomy and adjuvant RT. The patient with distant metastases was treated with chemotherapy (recurrences, Table 2).

The median DFS for the entire group was 42 months (11–128). Eight patients (8%) died at the end of the study (5 of them for reasons unrelated to breast cancer and 3 from an unknown cause).

On multivariate analysis, the only factor associated with improved DFS was tumor size smaller than 13 mm. The risk of disease recurrence or death was higher in patients with tumor sizes larger than 13 mm as opposed to less than or equal to 13 mm (HR=4.02, 95% CI 1.08–14.99, $p=0.04$). The HR for positive LVI was higher but did not reach statistical significance (HR=4.207, 95% CI 0.872–20.3, $p=0.07$). There was no statistically significant effect of other tumor-related factors, or systemic treatment on DFS.

Table 2 Recurrences

	number	Treatment upon recurrence						
Local recurrence	4	* Mastectomy only * Lumpectomy + SLNB + WBI (40.05 Gy/15Fx) * Two patients -Letrozole alone						
Locoregional recurrence	2	* Mastectomy + ALND + CW and low axilla RT (26 Gy/5Fx) * Lumpectomy + ALND and Breast + supra/axilla RT (40.05 Gy/15Fx and boost 13.35/5Fx)						
Distant recurrence	1	* Chemotherapy						
Recurred patient's characteristics at initial diagnosis								
Patient number	Age at cancer diagnosis (years)	Time to recurrence (months)	Histologic type	Tumor size (mm)	Margins at resection	LVI**	KI67**	Receipt of Endocrine treatment
1	80	68	Ductal	21	Negative	No	60	Yes
2	81	47	Ductal	15	Negative	-	10	Yes
3	87	57	Ductal	20	Negative	No	10	Yes
4	84	64	Ductal	7	negative	No	-	Yes
5	84	64	Mucinous	28	Negative	-	-	Yes
6	81	136	Ductal	13	Negative	No	12	Yes
7	91	47	Ductal	25	Negative	No	10	No

* SLNB Sentinel lymph node biopsy, WBI Whole breast irradiation, Fx Fraction, CW Chest wall

** 2 missing

Discussion

The treatment of breast cancer is continuously evolving. The main developments include screening, imaging, and a better understanding of biology, all contributing to personalized treatments. Population aging is a global phenomenon. The percentage of the population aged 65 and over increased from 6 to 9% between 1990 and 2019 and is expected to further increase [10]. There are numerous age-related chronic disorders including neurodegenerative diseases, cardiovascular diseases, immune system disorders, musculoskeletal disorders, and cancer [11]. The risk of cancer recurrence in elderly patients should be weighed against the potential morbidity and the quality of life (QoL) interference related to the therapy.

Treatment de-intensification is currently the practice in many fields of oncology. Many studies are showing the safety of omission of previously mandatory modalities such as surgery or radiation therapy in the treatment of different malignancies and breast cancer particularly. For instance, chemotherapy is no more indicated in early staged favorable prognostic, hormonal receptor-positive, HER2-negative breast cancer [12] and there is no benefit from completion of axillary lymph node dissection (ALND) in patients who presented with node negative disease and have limited nodal involvement according to SLNB [13].

(patients with favorable prognostic factors [3, 7] or when radiation treatment of regional lymphatics is planned [14]. The omission of RT is also widely recognized in a specific patient population [2, 3].

The omission of both radiation and SLNB raises the concern of increased risk of recurrence and impaired survival since clinically node-negative axilla have a 25–35% risk of harboring metastatic cells [15–17]. Our research showed that in a selected elderly patient population with HR-positive tumors which are smaller than 13 mm, the omission of both SLNB and adjuvant radiotherapy is feasible. Recurrence rate for the cohort was 7% (any recurrence), of the seven patients who experienced recurrence (6 LR and LRR and one distant recurrence) the disease was successfully treated in six.

We discuss herein the available data in the literature on the avoidance of RT, SLNB, and both in breast cancer.

Omission of radiation

The omission of radiation treatment in a highly selected population is well recognized (Table 3), [2, 3, 18–21]. The Prime II randomized trial demonstrated a local recurrence rate of 0.9% vs. 9.5% in the use of RT vs. no RT groups, respectively (HR 10.4, 95% CI 4.1–26.1, $p < 0.001$) with no difference in OS. The majority of

patients in this study underwent SLNB. The negative SLNB may account for the better results of LRR (0.5% vs., 2.3% regional recurrence). The CALGB 9343 study showed an axillary recurrence in the RT arm of 0% vs. 3% in the no RT arm (both arms received tamoxifen and 63% had no axillary surgery). Furthermore, the LUMINA trial, avoiding RT in younger HR-positive, HER2-negative patients with low Ki-67 (equal to or less than 13.25%) was associated with a 5-year LR of 2.3%. Attempts to incorporate additional biological markers into treatment de-intensification, including omission of RT were undertaken by numerous studies (Table 3), [22–27]. Finally, the NCCN guidelines allow BCS without adjuvant RT in elderly HR-positive, HER2-negative patients due to the lack of effect on OS and minimal impact on LR on those who did undergo RT (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). However, it is important to note that SLNB or ALND was standardly performed in the patients who participated in the above studies [3, 18–27].

Omission of SLNB

Martelli et al. reported in 2011 a low axillary recurrence (5.8%) in patients who did not have axillary surgery. Tumors less than 10 mm were associated with only 3.7% of axillary recurrences. There was no difference in OS between those with or without axillary dissection [7]. As 30% of patients received RT, this possibly complicates the interpretation of results since tangential field radiation of the breast leads to a substantial amount of incidental radiation dose to the low axilla (levels 1 and 2) [28].

The International Breast Cancer Study Group conducted in 2005 was a randomized study comparing QoL in a similar group of patients with or without axillary dissection. At a median follow-up of 6.6 years, there was no significant difference in DFS and OS with better QoL in women who did not have axillary surgery. In this trial, axillary recurrence was 1% and 3% with and without axillary surgery with 32% of patients in the non-axillary surgery group receiving adjuvant RT [29].

Gentilini et al. reported significantly higher early upper limb morbidity in patients who underwent SLNB vs. patients who did not with similar distant DFS at 5 years [8, 30].

The Intergroup Sentinel Mamma study (INSEMA) recently published QoL results of their randomized study assessing avoiding SLNB vs. SLNB or ALND. There was a clinical benefit regarding arm symptoms and functioning in patients who did not have an SLNB [31].

Liu et al. in a systemic review concluded that SLNB late morbidity including pain, impaired range of motion, edema, decreased strength, and sensory disorders is relatively rare, but should not be ignored [32]. Several trials

Table 3 Trials of radiotherapy omission in elderly early breast cancer patients

	Design	Age	Stage	ER/PR status	Axillary Surgery	Results LR		
NSABP B-21 [18]	RCT	ANY	T1a-bN0		AD	8y 16% vs. 3%		
Toronto-BC trial [19]	RCT	≥ 50	T1-2N0	NA	AD	8y 17.6% vs. 3.5%		
CALGB 9343 [3]	RCT	≥ 70	T1N0	ER-positive	AD or AS	12y 9% vs. 2%		
PRIME II [2]	RCT	≥ 65	T < 3 cm N0	ER/PR positive	AD or AS	10y 9.5% vs. 0.9%		
ABCSG 8 A [20]	RCT (2x2. With without tamoxifen. With/without radiation)	Post-menopausal	T ≤ 3 cm N0	ER/PR positive	AD	10y 7% vs. 2%		
BASO 2 [21]	RCT (2x2. With without tamoxifen. With/without radiation)	< 70	T1N0	ER/PR positive	AD or AS	5y 4% vs. 1%		
Trials of radiotherapy omission in early breast cancer patients incorporating biomarkers								
	Design	Age	Stage	ER/PR status	Axillary Surgery	Systemic treatment	Biomarker	Results LR
LUMINA [22]	Prospective Cohort	≥ 55	T1N0	ER/PR positive	SLNB or AD	Endocrine therapy	Ki67 ≤ 13.25%	5y 2.3%
IDEA [23]	Prospective Cohort	50-70	T1N0	ER/PR positive	SLNB or AD	Endocrine therapy	Oncotype RS ≤ 18	Completed accrual
PRECISION [24]	Prospective Cohort	50-75	T1N0	ER/PR positive	SLNB or AD	Endocrine therapy	PAM-50 low ROR	Completed accrual
UK PRIMETIME [25]	Prospective Cohort	≥ 60	T1N0	ER/PR positive	SLNB	Endocrine therapy	IHC4+C	Completed accrual
EXPERT [26]	Phase 3 RCT	≥ 50	T1N0	ER/PR positive	SLNB or AD	Endocrine therapy	PAM-50 low ROR ≤ 60	recruiting
DEBRA [27]	Phase 3 RCT	50-70	T1N0	ER/PR positive	SLNB or AD	Endocrine therapy	Oncotype Rs ≤ 18	recruiting

Table 4 Trials of SLNB omission

	Design		Age	Stage	ER/PR status	Breast radiotherapy	Results
SOUND [30]	RCT	SLNB Vs. no SLNB	any	cT1N0 (US)	any	yes	5y DFS 97.7% Vs. 98%
INSEMA [31]	RCT	SLNB vs. no SLNB	≥ 18	cT1-2N0	any	yes	Not recruiting
NAUTILUS [33]	RCT	SLNB vs. no SLNB	≥ 19	cT1-2N0 (US)	any	yes	recruiting
BOOG 2013–08 [34]	RCT	SLNB vs. no SLNB	≥ 18	cT1-2N0 (PE + US)	any	Yes	recruiting
SOAPET (https://classic.clinicaltrials.gov/show/NCT04072653)	Single group	no SLNB	≥ 18	cT1-2N0 (PE + US. LymphPET)	any	Yes	recruiting

investigating SLNB vs. no SLNB in clinically node-negative women are ongoing, and adjuvant breast radiotherapy is mandatory in their protocols (Table 4), [30, 31, 33, 34] (<https://classic.clinicaltrials.gov/show/NCT04072653>).

The reasonable question arising in clinical practice is whether the omission of both modalities, RT and axillary surgery is feasible considering the risk of recurrence vs. the benefit in reducing toxicity from these procedures. There are few studies in the literature which address this issue. Zhong Y et al. in 2020 published the results of a retrospective study showing the acceptable low risk of recurrence in omitting both modalities with no difference in DFS [35]. On the contrary, a recent meta-analysis showed that the omission of axillary surgery to stage the axilla may be associated with a higher risk of overall mortality in older women with early-stage breast cancer compared to those who did undergo axillary surgery [17].

The results of our research support the evolving approach of de-intensification in the treatment of breast cancer in elderly patients with good prognostic features. Only two patients out of 100 in our retrospective analysis developed LRR. They were subsequently salvaged by ALND and RT (Table 2). We also showed a significant correlation between tumor size (more or less than 13 mm) and DFS. Clinicians are encouraged to use this data when discussing the benefits and side effects of adjuvant RT and SLNB in early breast cancer.

We recognize the limitations of a single-center retrospective cohort with inherent biases. However, given the paucity of evidence available regarding the omission of both treatment modalities in this selected patient population, it adds to the data supporting the decision to safely de-escalate treatment and spare toxicity. Given the biology of HR-positive tumors, a longer follow-up period time will allow for a more comprehensive understanding of the results.

Conclusions

The results of our study suggest that omission of both SLNB and adjuvant RT is safe in early HR-positive, HER2-negative elderly breast cancer patients with acceptable LRR. Tumor size less than 13 mm is associated with better DFS. This data can facilitate clinicians when discussing treatment options.

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Authors' contributions

Y.K. - conception, design of the work, acquisition, analysis, interpretation of data, drafted the work and revised it. M.K. - conception, design of the work, acquisition. H.G. and I.W. and V.S. - drafted the work or revised it. Y.H. and A.N. - analysis. All authors approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by Tel Aviv Sourasky Medical Center's institutional ethics committee.

As data were analyzed anonymously, no consent was required.

Competing interests

The authors declare no competing interests.

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