Elderly Breast Cancer Patients Benefit from Surgery According to Guidelines

Mathias Kvist Mejdahl (mathias.kvist.mejdahl@regionh.dk)
Copenhagen University Hospital Herlev https://orcid.org/0000-0002-4286-1533

Mette Haulund Christensen
Copenhagen University Hospital Herlev and Gentofte

Birgitte Paaschburg Nielsen
Copenhagen University Hospital Herlev and Gentofte

Tove Holst Filtenborg Tvedskov
Copenhagen University Hospital Herlev and Gentofte

Research Article

Keywords: Elderly women, primary endocrine treatment, breast cancer survival

Posted Date: June 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-579534/v1

Abstract

Purpose

To investigate among women ≥ 70 years with early stage invasive breast cancer, whether primary endocrine therapy and omission of surgery resulted in an inferior relative survival, whether the omission of preoperative imaging resulted in an inferior local control, and whether the omission of axillary staging resulted in an inferior regional control and inferior relative survival.

Methods

A single center retrospective cohort study at Herlev Hospital, Denmark. Relative survival was expressed as standardized mortality ratios (SMR) and differences were estimated using Poisson regression and evaluated by rate ratios (RR). Differences in local and in regional recurrence were estimated by a Cause Specific Hazard Model and evaluated by hazard ratios (HR). Models were adjusted for age, comorbidity, and tumor size.

Results

We identified 1,142 women. Patients who received only endocrine therapy had a higher SMR than patients treated with primary surgery (RR = 2.57;95%CI:2.01–3.30). Patients treated with primary breast conserving surgery (BCS) did not have a lower risk of local recurrence if they received preoperative imaging (HR = 0.88;95%CI:0.27–2.81). Finally, patients who received an axillary staging had a lower risk of regional recurrence compared to patients who did not receive axillary surgery (HR = 0.25;95%CI:0.08–0.84), but not a statistically significant superior relative survival (RR = 0.78;95%CI:0.60-1.00).

Conclusion

Elderly women with early stage breast cancer treated with only endocrine therapy had an inferior relative survival, omission of axillary staging resulted in a higher risk of regional recurrence and a tendency to an inferior relative survival, and omission of preoperative imaging before BCS did not result in a higher risk of local recurrence.

Background

With the increased life expectancy, the number of elderly women diagnosed with primary invasive breast cancer is growing. In the United States from 2012–2016, 31% of incident breast cancer cases among women were 70 years or older [1]. Still, there is a lack of level 1 evidence on treatment recommendations for this group of patients, and treatment guidelines are often based on smaller subgroup analyses or extrapolations from results on younger individuals [2]. It has been demonstrated that elderly breast

cancer patients more often receive less aggressive treatment than younger breast cancer patients [3,4], which can be partly explained by them having a higher degree of comorbidity, high age itself, and also because of patient preference [5]. Women above 70 years diagnosed with breast cancer have a poorer relative survival compared to younger women, and it has been suggested that this is due to non-adherence to guidelines resulting in inferior treatment [6]. Substantiating this, omission of surgery in elderly women with primary invasive breast cancer has been shown in several studies to result in inferior breast cancer survival [7,5,8]. Instead of primary surgical treatment of operable breast cancer, some older women are treated with primary endocrine therapy, which was first described in the early 80's as an alternative treatment option for older women with primary invasive breast cancer [9,10]. This treatment is however in most guidelines not considered standard of care, and a systematic Cochrane review from 2014 concluded that *'primary endocrine therapy should only be offered to women with oestrogen receptor (ER)-positive tumours who are unfit for surgery, at increased risk of serious surgical or anaesthetic complications if subjected to surgery, or who refuse surgery.'* [11]. With the advancements in less invasive surgical techniques (e.g. sentinel lymph node biopsy and increased use of breast conserving surgery) and higher safety in anesthetic procedures, today even patients with several comorbidities would be fit for a surgical intervention for invasive primary breast cancer.

Axillary surgery in clinically node negative elderly patients has shown to reduce the risk of regional recurrence, but doesn't seem to have an effect on overall or breast cancer specific mortality [12,13]. Therefore the SIOG/EUSOMA guidelines, although recommending sentinel lymph node biopsy (SLNB) as standard of care in clinically node negative elderly breast cancer patients, does state that '*omission of SLNB and completion ALND might be reasonable in some older patients*'[2], and the American Choosing Wisely initiative have gone even further in their recommendations, stating that axillary staging safely can be omitted in clinically node negative patients above 70 years with HER2 negative and estrogen receptor positive breast cancer [14].

In the Danish Breast Cancer Group (DBCG) guidelines, the 'triple test' (clinical examination, diagnostic imaging (ultrasound and mammography) and fine needle aspiration or core needle biopsy) is regarded as the cornerstone in the diagnostic investigation of breast cancer [15]. Further, leaving out mammography from the diagnostic investigation of patients, should only be considered if patients are younger than 30 years, if the patient is pregnant or is breast feeding, or if the patient has inflammation of the breast [15]. Despite these guidelines, it is our experience, that elderly breast cancer patients often do not receive a mammography as part of the diagnostic evaluation.

The aims of the present study were, in a single center retrospective cohort study of women 70 years or older diagnosed with early stage primary invasive breast cancer, to examine whether primary endocrine therapy instead of primary surgery resulted in an inferior relative survival, whether the omission of preoperative imaging resulted in an inferior local control, and whether the omission of the sentinel lymph node biopsy resulted in an inferior regional control and an inferior relative survival.

Methods

Study design and study population

The present study is a single center retrospective cohort study. All women, ≥ 70 years old, diagnosed with primary invasive breast cancer and treated at the Department of Breast Surgery at Herlev Hospital, Denmark, from March 2000 until December 2007 were included in the cohort. First, we looked at the relative survival according to whether patients had been surgically treated, treated only with primary endocrine therapy, or treated with primary endocrine therapy followed by surgical treatment. Patients who received neoadjuvant chemotherapy or who received neither surgery nor endocrine therapy were excluded. Secondly, we looked at the risk of local recurrence according to whether patients treated with breast conserving surgery (BCS) had received preoperative imaging. Patients treated with a mastectomy, patients receiving neoadjuvant treatment, and patients not receiving surgical treatment were excluded. Finally, the risk of regional recurrence as well as the relative survival was investigated among clinically node negative surgically treated patients according to whether they did not receive axillary surgery or whether they were treated with SLNB. Patients who were not surgically treated or who received neoadjuvant therapy were excluded. Patients directly treated with axillary lymph node dissection (ALND) would have either clinically evident metastasis to the axilla, metastasis visualized on ultrasound, or biopsy verified metastasis and were considered as clinically node positive and excluded as well.

Variables

Data on demographics, surgical and oncological treatment, histopathology, comorbidity, recurrences and mortality was retrieved through medical records. The medical records are linked to the Danish civil registration system, and therefore data on mortality is automatically updated in the medical files. Data on the background mortality among Danish women was retrieved from Statistics Denmark [16].

For histopathology, data on tumor histology, malignancy grade of invasive ductal carcinomas, tumor size, estrogen receptor status, and number of metastases to the axilla was registered. Comorbidity was quantified using the Charlson Comorbidity Index (CCI) [17]. In the multivariable analyses, tumor size was categorized into 1-20mm and > 20mm, CCI was categorized into 0, 1, and > 1, and age was categorized into 70–74 years, 75–79 years, 80–84 years, and ≥ 85 years.

Outcomes

Follow-up on mortality was recorded up until between March and August 2017. Follow-up on local recurrence, regional recurrence, distant metastasis, or contralateral breast cancer was recorded until either an event, death or last clinical follow-up, whichever came first.

Statistical analysis

Data on demographics, disease characteristics, comorbidity, and treatment were evaluated and presented descriptively with counts and percentages.

In the analysis investigating the effect of primary treatment on relative survival, patients were divided into three groups: surgery as primary treatment, endocrine treatment as only treatment, and endocrine

treatment as primary treatment followed by surgery. Standardized mortality ratios (SMR) were used as a measure of breast cancer related death. SMRs were calculated as the observed overall mortality rate among our patients divided by the expected mortality rate within strata of 1 year age groups, 5 year calendar period, and 1 year intervals since time of diagnosis. The expected mortality rates were the background mortality rates among women in Denmark. Differences in SMRs between groups were estimated by Poisson Regression and evaluated by rate ratios (RR). The Poisson model was adjusted for tumor size, age in 5 year groups, CCI, time since diagnosis (in 1 year groups), and time period. We tested for interaction between age and the three primary treatment groups.

In the analysis investigating the effect of preoperative imaging on local control, patients were divided into two groups: preoperative imaging and no preoperative imaging. The outcome was time until local recurrence, censoring on 'last follow-up contact', regional recurrence, distant metastasis, contralateral disease, or death whichever came first. Differences in local recurrences were estimated by a Cause specific hazards model and evaluated by cause specific hazard ratios (HR). Proportionality was assessed graphically using Martingale residuals and statistically with the supremum test. The model was adjusted for age, comorbidity, and tumor size.

In the analysis investigating the effect of primary axillary surgery on regional control and relative survival, patients were divided into two groups: no axillary surgery and SLNB. For regional control, the outcome was time until regional recurrence, censoring on 'last follow-up contact', local recurrence, distant metastasis, contralateral disease, or death whichever came first. Differences in regional recurrences were estimated by a Cause specific hazards model and evaluated by cause specific hazard ratios (HR). Proportionality was assessed graphically using Martingale residuals and statistically with the supremum test. The model was adjusted for age and comorbidity. For relative survival, a poisson model was used as described above, adjusting for age, comorbidity, time period and time since diagnosis.

Alpha was set at 0.05. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC).

Results

Between March 2000 and December 2007, 1,142 patients ≥ 70 years were treated for primary invasive breast cancer at the Department of Breast Surgery, Herlev and Gentofte Hospital. The median age was 77 years (Interquartile range: 73–82). For overall mortality, the median follow-up was 7.80 years (IQR: 3.94–11.36), with 795 (69.6%) dying during follow-up. For recurrence the median follow-up was 6.25 years (IQR: 2.51–10.15). 52 were registered with local recurrence and 39 with regional recurrence. Patient and disease characteristics are presented in Table 1, and treatment characteristics are presented in Table 2 according to age.

Primary surgery or endocrine therapy as monotherapy and breast cancer related death

Among 1,142 patients, 13 received neoadjuvant chemotherapy and two patients had missing data on surgery or were not treated with either surgery or endocrine therapy, leaving 1,127 patients (see Fig. 1). Of the 1,127 patients, 969 (86%) received surgery as the primary treatment, 57 (5%) received endocrine therapy followed by surgery, and 103 (9%) patients received endocrine therapy alone. Among the 57 patients receiving primary endocrine therapy followed by surgery, the median time from diagnosis to surgery was 228 days (IQR: 129–371). The observed and expected survival according to primary treatment is presented in Fig. 2. The SMR among patients receiving endocrine therapy alone was significantly increased compared to patients receiving surgery as primary treatment with a RR on 2.57 (95% CI: 2.01–3.30). No increased risk was found for patients receiving primary endocrine therapy followed by surgery, where the RR was 1.23 (95% CI: 0.91–1.66) (see Table 3). There was a statistically significant interaction between age and primary treatment, with the effect of receiving only endocrine therapy vs primary surgery on the SMR being particularly elevated in the patient group 70–74, RR = 25.42 (95% CI: 7.63–84.67). For all other age groups, the RRs were similar, ranging from 2.36 to 2.68.

Preoperative imaging and risk of local recurrence

580 patients were included in the analysis, excluding 175 patients treated with neoadjuvant therapy and 387 patients treated with a mastectomy (see Fig. 1). Among the 580 patients, 319 received preoperative imaging, 253 patients did not receive preoperative imaging planning, and 8 patients had missing data. The adj. HR for local recurrence among patients receiving preoperative imaging vs not receiving preoperative imaging was 0.88 (95% CI: 0.27–2.81) (see Table 3).

Sentinel lymph node biopsy and risk of regional recurrence

Of the 1142 patients, 342 clinically node positive patients treated with ALND and 175 patients treated with neoadjuvant therapy were excluded (see Fig. 1). Among 625 clinically node negative patients included in the analysis, 197 patients were not treated with axillary surgery and 428 patients were staged by a SLNB. Of the latter 428 patients, 141 patients had a completion ALND. Among the 287 patients who did not receive an ALND after sentinel lymph node staging, 229 (80%) had no metastases, 16 (6%) had isolated tumor cells, 28 (10%) had only micrometastases, and 13 (5%) had macrometastases in the sentinel node. There was missing data on nodal status for one patient. Patients who were staged by SLNB had a lower risk of regional recurrence compared with patients who did not have axillary surgery (adj. HR = 0.25; 95% CI: 0.08–0.84; p = 0.02) (see Table 3). Further, there was a tendency to a superior relative survival among patients who were staged by SLNB (RR = 0.78; 95% CI: 0.60-1.00; p = 0.05).

Discussion

In the present study we found that women more than 70 years old, diagnosed with primary invasive early stage breast cancer, have an inferior relative survival if they are treated with endocrine therapy alone compared with women treated with primary surgery. Further, omission of axillary surgery in clinically node negative patients resulted in a higher risk of regional recurrence, and a tendency to an inferior relative survival. Use of preoperative imaging in this patient group did not seem to result in a better local control.

In a systematic review by the Cochrane Collaboration from 2014, seven randomized trials were identified comparing primary surgery with primary endocrine therapy for elderly women with operable breast cancer. They showed that surgery with adjuvant endocrine therapy resulted in better local control and a tendency to better overall survival than endocrine therapy alone. There was no difference in overall survival in studies comparing surgery alone with endocrine therapy alone [11]. A review from 2017 by Pepping et al however concluded that no difference in overall survival was observed comparing primary endocrine therapy with primary surgery, and they recommended that primary endocrine therapy should be considered for patients with a life expectancy of less than two years and for frail patients especially with low risk tumors [8]. Since these reviews some observational studies have demonstrated that omission of surgery is associated with an inferior overall survival: A Danish observational study by Vogsen et al including 5,856 patients ≥ 70 years diagnosed between 2008 and 2012 showed that omission of surgery among elderly women with early stage breast cancer was associated with an inferior overall survival, and in an interaction analysis this association was significantly more pronounced among women less than 80 years [5]. Interestingly, they further showed that the main reason for deviating from treatment guidelines was patient request [5]. A large British observational study including 23,849 patients diagnosed between 2002–2010 also showed that omission of surgery among elderly women with early stage ER positive breast cancer was associated with a significantly inferior breast cancer specific survival [7]. Our results are in line with these two recent studies. Despite these results it can however be argued that even though we adjust for age and comorbidity using the CCI, some of the effect of primary endocrine therapy on survival can be explained by residual confounding of comorbidity or unmeasurable 'frailty'. In the SIOG/EUSOMA guidelines from 2012 they recommend that *"Primary endocrine therapy should only be offered to elderly individuals with ER-positive tumours who have a short estimated life expectancy (< 2–3 years), who are considered unfit for surgery after optimisation of medical conditions or who refuse surgery. The involvement of a geriatrician is strongly recommended to estimate life expectancy and guide management of reversible comorbidities. It is reasonable to choose tamoxifen or an aromatase inhibitor based on potential side-effects."* [2]. It should be noted, that among all our patients only 9% received primary endocrine therapy alone during the seven-year period from 2000 to 2007. This number is considerably lower than the 15% observed in a Danish study looking at all women ≥ 70 years treated for early stage breast cancer between 2008 and 2012 [5], and even lower than what has been observed across several European countries [18]. We could, based on these numbers, conclude that undertreatment with primary endocrine therapy alone at our institution is relatively uncommon.

In the present study we found that omission of axillary surgery in clinically node negative patients was associated with a higher risk of regional recurrence. This is in line with a recent meta-analysis [12]. This meta-analysis further showed that omission of axillary surgery in clinically node negative elderly patients did not have an impact on survival, neither overall nor breast cancer specific [12]. It should be noted that the meta-analysis was only based on two RCT's [19,20]. Given that axillary surgery in previous studies have had no impact on survival, the Choosing Wisely initiative has recommended that '*Patients ≥ 70 years of age with early stage hormone receptor positive, HER2 negative breast cancer and no palpable axillary lymph nodes can be safely treated without axillary staging*' [14]. This recommendation has

however raised some debate among American Breast Cancer Surgeons [21]. Notwithstanding this, a recent American study did show, that since the publication of the Choosing Wisely recommendations, a significant decline in the use of sentinel lymph node biopsies in women older than 70 years has been observed [22]. In our study there was a tendency towards better relative survival among patients who received axillary surgery, although the result was not statistically significant. Besides the effect on regional control, axillary staging is important for the decision on adjuvant treatment. In a study by Tamirisa et al it was demonstrated that elderly breast cancer patients were less likely to receive adjuvant treatment if they did not receive axillary surgery and thus have an inferior survival [23]. This could argue for the use of sentinel lymph node biopsy for staging purposes also among elderly patients.

We were not able to show, that the preoperative omission of mammography and ultrasound in patients treated with breast conserving surgery resulted in a higher risk of local recurrence. It should be noted though, that only 52 patients were registered with local recurrence which should caution any conclusions on whether preoperative imaging can safely bee omitted among these patients. Still, our results do suggest that among elderly women with early stage breast cancer, treated with breast conserving surgery, the omission of preoperative imaging for surgical planning might be a safe solution for certain patients.

The most important limitation to the present study is the risk of confounding, not accounted for. Residual confounding of comorbidity is notably a problem, as it is not unreasonable to assume that the Charlson Comorbidity Index does not capture the full picture of comorbidity and ‘frailty’ among our patients. At worst, all the effect of omitting surgery would be explained by residual comorbidity and frailty. However, if all patients treated primarily with primary endocrine therapy could be regarded as having the same comorbidity and frailty, the difference between patients receiving surgery at a later stage, and the patients who never receive surgery could be regarded as the ‘true’ effect of surgery on survival. As the RR for the first mentioned group is 1.23 and the latter is 2.57, the effect of surgery on survival would still be large. The strengths of our study are that we have very few missing data, and very complete follow-up data on our patients.

In conclusion, our study has demonstrated that treating elderly women with early stage breast cancer with only endocrine therapy is associated with an inferior relative survival, that omitting staging by the sentinel lymph node biopsy results in a higher risk of regional recurrence and a tendency to inferior relative survival, and that omitting preoperative imaging before breast conserving surgery does not result in a higher risk of local recurrence.

Declarations

Funding: the present study did not receive any funding

Conflicts of interest: All authors declare no conflicts of interest regarding the present topic

Author’s contributions: MHC and BPN collected the data, all authors contributed to the conception and design of the study, MKM conducted the statistical analyses and wrote the first draft, THFT revised the

first draft of the manuscript, and all authors contributed to the revision of the manuscript, and all authors approved the final draft of the manuscript.

Ethics approval: the study was approved by the Danish data protection agency.

All authors consent to the publication of the study.

References

1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL (2019) Breast cancer statistics, 2019. CA Cancer J Clin 69 (6):438–451. doi:10.3322/caac.21583
2. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R (2012) Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 13 (4):e148-160. doi:10.1016/S1470-2045(11)70383-7
3. Evron E, Goldberg H, Kuzmin A, Gutman R, Rizel S, Sella A, Gutman H (2006) Breast cancer in octogenarians. Cancer 106 (8):1664–1668. doi:10.1002/cncr.21788
4. Litvak DA, Arora R (2006) Treatment of elderly breast cancer patients in a community hospital setting. Arch Surg 141 (10):985–990; discussion 990. doi:10.1001/archsurg.141.10.985
5. Vogsen M, Bille C, Jylling AMB, Jensen MB, Ewertz M, Academy for Geriatric Cancer R (2020) Adherence to treatment guidelines and survival in older women with early-stage breast cancer in Denmark 2008–2012. Acta Oncol 59 (7):741–747. doi:10.1080/0284186X.2020.1757148
6. Jensen JD, Cold S, Nielsen MH, Jylling AM, Soe KL, Larsen LB, Ewertz M, Academy of Geriatric Cancer R (2016) Trends in breast cancer in the elderly in Denmark, 1980–2012. Acta Oncol 55 Suppl 1:59–64. doi:10.3109/0284186X.2015.1115118
7. Ward SE, Richards PD, Morgan JL, Holmes GR, Broggio JW, Collins K, Reed MWR, Wyld L (2018) Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. Br J Surg 105 (11):1454–1463. doi:10.1002/bjs.10885
8. Pepping RMC, Portielje JEA, van de Water W, de Glas NA (2017) Primary Endocrine Therapy in Older Women with Breast Cancer. Curr Geriatr Rep 6 (4):239–246. doi:10.1007/s13670-017-0223-z
9. Bradbeer JW, Kyngdon J (1983) Primary treatment of breast cancer in elderly women with Tamoxifen. Clin Oncol 9 (1):31–34
10. Preece PE, Wood RA, Mackie CR, Cuschieri A (1982) Tamoxifen as initial sole treatment of localised breast cancer in elderly women: a pilot study. Br Med J (Clin Res Ed) 284 (6319):869–870. doi:10.1136/bmj.284.6319.869-a
11. Morgan J, Wyld L, Collins KA, Reed MW (2014) Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database of Systematic Reviews (5). doi:10.1002/14651858.CD004272.pub3

12. Liang S, Hallet J, Simpson JS, Tricco AC, Scheer AS (2017) Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: A systematic review and meta-analysis. J Geriatr Oncol 8 (2):140–147. doi:10.1016/j.jgo.2016.12.003
13. Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, Agresti R (2011) Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol 18 (1):125–133. doi:10.1245/s10434-010-1217-7
14. Choosing Wisely Initiative Recommendation for Sentinel node biopsy in patients 70 years or more. https://www.choosingwisely.org/clinician-lists/sso-sentinel-node-biopsy-in-node-negative-women-70-and-over/.
15. DBCG Guidelines for Diagnostic Investigation. https://dbcg.dk/PDF/Kap_2_Diagnose_24.05.2013.pdf.
16. Statistikbanken. Statistics Denmark. http://www.statistikbanken.dk/statbank5a/default.asp?w=1920. Accessed 01-11-2019
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40 (5):373–383. doi:10.1016/0021-9681(87)90171-8
18. Derks MGM, Bastiaannet E, Kiderlen M, Hilling DE, Boelens PG, Walsh PM, van Eycken E, Siesling S, Broggio J, Wyld L, Trojanowski M, Kolacinska A, Chalubinska-Fendler J, Goncalves AF, Nowikiewicz T, Zegarski W, Audisio RA, Liefers GJ, Portielje JEA, van de Velde CJH, Group EBC (2018) Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer 119 (1):121–129. doi:10.1038/s41416-018-0090-1
19. Martelli G, Boracchi P, Orenti A, Lozza L, Maugeri I, Vetrella G, Agresti R (2014) Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. Eur J Surg Oncol 40 (7):805–812. doi:10.1016/j.ejso.2014.03.029
20. International Breast Cancer Study G, Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, Rey P, Dent D, Campbell I, Bernhard J, Price KN, Castiglione-Gertsch M, Goldhirsch A, Gelber RD, Coates AS (2006) Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10–93. J Clin Oncol 24 (3):337–344. doi:10.1200/JCO.2005.01.5784
21. Blair SL, Tsai C, Tafra L (2018) ASBRS Great Debate: Sentinel Node Biopsy in Patients Over 70 Years of Age. Ann Surg Oncol 25 (10):2813–2817. doi:10.1245/s10434-018-6617-0
22. Calderon E, Webb C, Kosiorek HE, Richard JGMD, Cronin P, Anderson K, Northfelt D, McCullough A, Ocal IT, Pockaj B (2019) Are we choosing wisely in elderly females with breast cancer? Am J Surg 218 (6):1229–1233. doi:10.1016/j.amjsurg.2019.08.004
23. Tamirisa N, Thomas SM, Fayanju OM, Greenup RA, Rosenberger LH, Hyslop T, Hwang ES, Plichta JK (2018) Axillary Nodal Evaluation in Elderly Breast Cancer Patients: Potential Effects on Treatment

Decisions and Survival. Ann Surg Oncol 25 (10):2890–2898. doi:10.1245/s10434-018-6595-2

Tables

Table 1: Patient and disease characteristics and demographics of 1142 elderly breast cancer patients treated between 2000 - 2007

Age group, N (%)	
70-74 years	425 (37.2)
75-79 years	297 (26.0)
80-84 years	221(19.4)
85-89 years	144 12.6)
≥90 years	55 (4.8)
Year of diagnosis, N (%)	
2000	99 (8.7)
2001	130 (11.4)
2002	160 (14.0)
2003	166 (14.5)
2004	144 (12.6)
2005	146 (12.8)
2006	154 (13.5)
2007	143 (12.5)
Charlson Comorbidity Index, N (%)	
0	641 (57.8)
1	302 (27.2)
2	113 (10.2)
≥3	54 (4.9)
Missing	32
Histology	
Invasive ductal carcinoma	734 (72.6)
Grade I	218 (21.6)
Grade II	378 (37.4)
Grade III	137 (13.6)
Grade missing	1 (0.1)
Invasive lobular carcinoma	167 (16.5)
Other	110 (10.9)

Missing*	131
Estrogen receptor status	
Positive	981 (86.5)
Negative	153 (13.5)
Missing	8
Tumor size	
≤10mm	123 (10.9)
11-20mm	415 (36.9)
21-50mm	500 (44.5)
>50mm	86 (7.7)
Missing	18
Lymph node involvement	
0 metastaser	600 (58.3)
Only micro metastases	67 (6.5)
1-3 macro metastases	208 (20.2)
4-9 macro metastases	87 (8.4)
≥10 macro metastases	68 (6.6)
Missing	112

*51 had missing histology due to inoperable/ulcerated cancer, 57 declined surgery.

Table 2: Treatment characteristics of according to age groups of 1142 elderly breast cancer patients treated between 2000 - 2007, N (%)

Age groups	All	70-74 y	75-79 y	80-84 y	85-89 y	≥90 y
Surgery of the breast						
Breast conserving surgery	618 (54.2)	223 (52.5)	179 (60.3)	125 (56.8)	76 (52.8)	15 (27.3)
Mastectomy	408 (35.8)	191 (44.9)	95 (32.0)	67 (30.5)	41 (28.5)	14 (24.5)
No surgery	104 (9.1)	4 (0.9)	19 (6.4)	28 (12.7)	27 (18.6)	26 (47.3)
Type of surgery not disclosed	11 (1.0)	7 (1.7)	4 (1.4)	0	0	0
Missing	1					
Axillary surgery						
No axillary surgery	326 (28.6)	23 (5.4)	64 (21.6)	94 (42.7)	95 (66.0)	50 (90.9)
SLNB only	287 (25.2)	156 (36.7)	69 (23.2)	52 (23.6)	9 (6.3)	1 (1.8)
SLNB followed by ALND	141 (12.4)	92 (21.7)	39 (13.1)	8 (3.6)	2 (1.4)	0
ALND	387 (33.9)	154 (36.2)	125 (42.1)	66 (30.0)	38 (26.4)	4 (7.3)
Missing	1					
Primary/neoadjuvant systemic treatment						
No	967 (84.8)	396 (93.2)	263 (88.6)	181 (82.3)	102 (70.8)	24 (45.5)
Yes	174 (15.3)	29 (6.8)	34 (11.5)	39 (17.7)	42 (29.2)	30 (54.6)
Primary Tamoxifen alone	64 (36.8)	3 (10.3)	6 (17.6)	18 (46.2)	17 (40.5)	20 (66.7)
Primary Tamoxifen followed by surgery	1 (0.6)	1 (3.4)	0	0	0	0
Primary Aromatase Inhibitor alone	39 (22.4)	1 (3.4)	12 (35.3)	10 (25.6)	10 (23.8)	6 (20.0)
Primary Aromatase Inhibitor followed by surgery	5 (2.9)	2 (6.9)	3 (8.8)	0	0	0
Primary endocrine therapy followed by surgery[a]	51 (29.3)	11 (37.9)	10 (29.4)	11 (28.2)	15 (35.7)	4 (13.3)
Neoadjuvant chemotherapy	13 (7.5)	11 (37.9)	2 (5.9)	0	0	0

Radiotherapy as monotherapy	1 (0.6)	0	1 (2.9)	0	0	0
Adjuvant therapy						
Chemotherapy						
Yes	19 (1.7)	14 (3.3)	4 (1.4)	0	1 (0.7)	0
No	1100 (98.3)	407 (96.7)	292 (98.7)	215 (100)	139 (99.3)	47 (100)
Radiotherapy						
Yes	340 (30.4)	264 (62.7)	64 (21.6)	9 (4.2)	3 (2.1)	0
No	779 (69.6)	157 (37.3)	232 (78.4)	206 (95.8)	137 (97.9)	47 (100)
Endocrine therapy						
Tamoxifen	492 (44.0)	189 (44.9)	128 (43.2)	91 (42.3)	63 (45.0)	21 (44.7)
Tamoxifen+aromatase inhibitor	105 (9.4)	32 (7.6)	33 (11.2)	22 (10.2)	14 (10.0)	4 (8.5)
Aromatase inhibitor	161 (14.4)	61 (14.5)	37 (12.5)	34 (15.8)	20 (14.3)	9 (19.2)
No endocrine therapy	361 (32.3)	139 (33.0)	98 (33.1)	68 (31.6)	43 (30.7)	13 (27.7)
Missing	23					
Preoperative imaging, N (%)						
No preoperative imaging	500 (44.3)	28 (6.7)	156 (53.2)	156 (71.6)	112 (78.9)	48 (88.9)
Mammography + ultrasound	618 (54.8)	392 (93.1)	135 (46.1)	58 (26.6)	29 (20.4)	4 (7.4)
Only ultrasound	10 (0.9)	1 (0.2)	2 (0.7)	4 (1.8)	1 (0.7)	2 (3.7)
Missing	14					

[a]Not disclosed whether patients received Tamoxifen or Aromatase Inhibitor

Table 3. Relative survival according to primary treatment and use of SLNB. Risk of local recurrence according to preoperative imaging and risk of regional recurrence according to SLNB.

	RR[a] (95% CI)	P-value	HR[b] (95% CI)	P-value
Surgery[c]	[Ref]	<0.01		
Endocrine therapy plus surgery	1.23 (0.91-1.66)			
Endocrine therapy alone	2.57 (2.01-3.30)			
No preoperative imaging[d]			[Ref]	0.82
Preoperative imaging			0.88 (0.27-2.81)	
No surgery of the axilla[e]	[Ref]	0.05	[Ref]	0.02
SLNB	0.78 (0.60-1.00)		0.25 (0.08-0.84)	

[a] Rate ratio of differences in relative survival using standardized mortality ratios.

[b] Cause specific hazard ratio. For preoperative imaging, the cause specific hazard of local recurrence is presented. For SLNB, the cause specific hazard of regional recurrence is presented.

[c] Adjusted for age, comorbidity, tumor size, time period, and time since diagnosis.

[d] Adjusted for age, comorbidity, adjuvant radiotherapy and tumor size.

[e] Adjusted for age, comorbidity, and tumor size in the cause specific hazards model, and further for time period, and time since diagnosis in the poisson model.

Figures

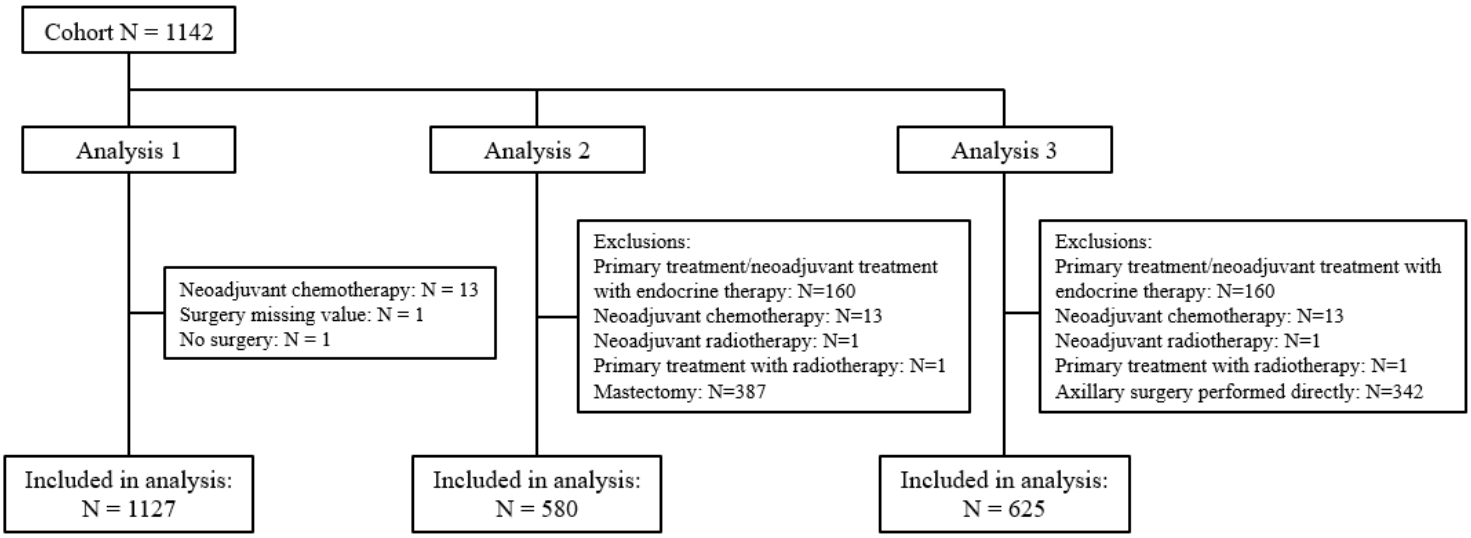

Figure 1

Flowchart according to study aims. Analysis 1: relative survival according to primary treatment with surgery vs endocrine therapy. Analysis 2: risk of local recurrence according to preoperative imaging vs no preoperative imaging. Analysis 3: risk of regional recurrence and relative survival according to the use of axillary staging with the SLNB procedure in surgically treated patients.

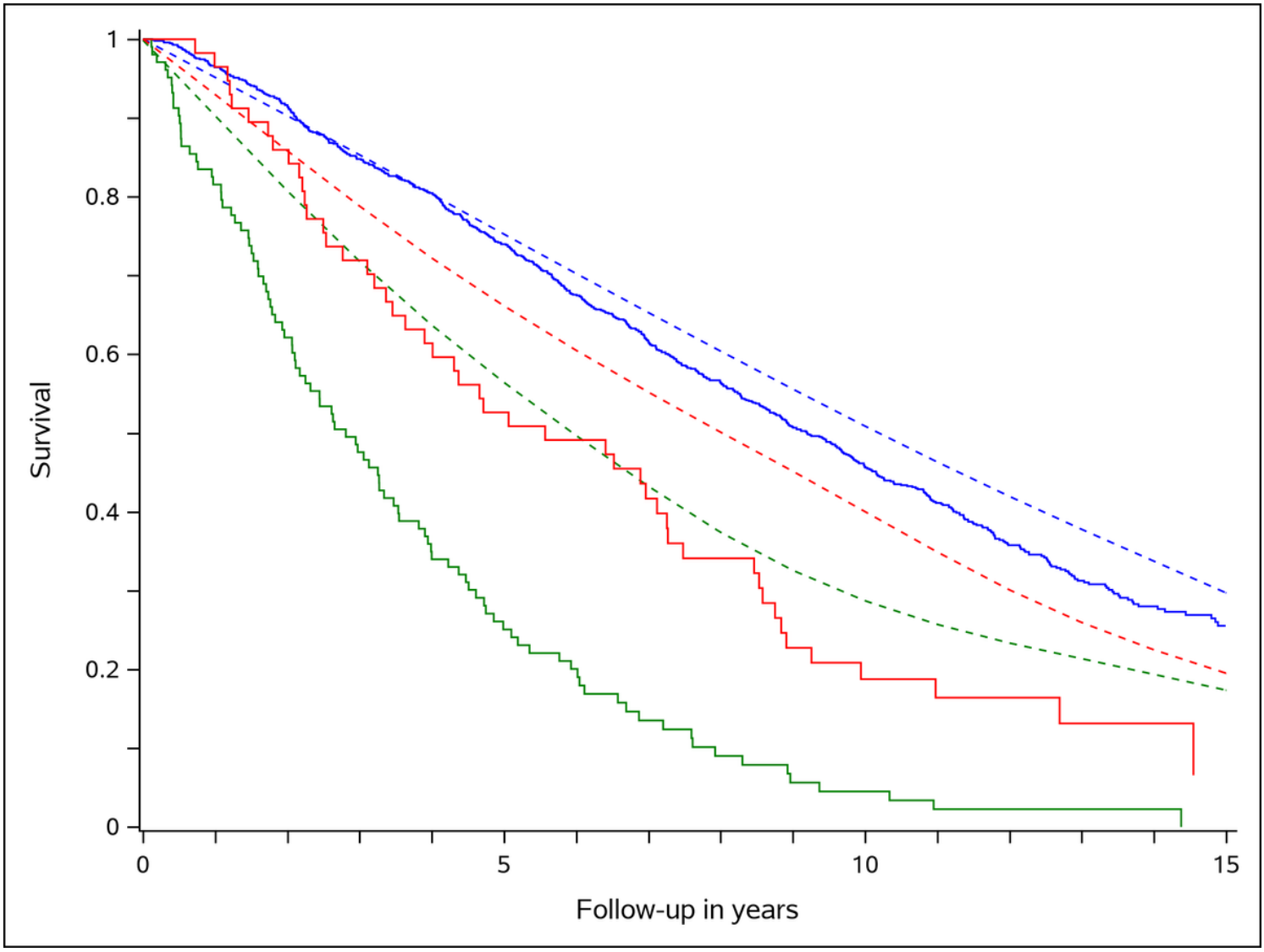

Figure 2

Observed overall and expected survival according to primary treatment. Blue solid line: overall mortality among patients treated primarily with surgery. Blue dashed line: expected mortality among patients treated primarily with surgery. Red solid line: overall mortality among patients treated primarily with endocrine therapy followed by surgery. Red dashed line: expected mortality among patients treated primarily with endocrine therapy followed by surgery. Green solid line: overall mortality among patients treated with endocrine therapy alone. Green dashed line: expected mortality among patients treated with endocrine therapy alone.