"Long-term follow up of axillary recurrences after negative Sentinel Lymph Node Biopsy; effect on prognosis and survival"

Running head: Axillary recurrences after negative SLNB

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Keywords: Breast cancer, Sentinel lymph node biopsy, Axillary recurrence, prognosis

Abstract

Background: As axillary recurrence (AR) after a negative sentinel lymph node biopsy (SLNB) is rare, the prognosis of these patients is unknown. Since treatment paradigms for patients with breast cancer are shifting towards less axillary surgery, the number of ARs might increase. In this study we evaluated primary and salvage treatment as well as long term survival of patients diagnosed with an AR.

Patients and methods: A retrospective analysis of the cancer registry of 16 breast cancer units in the Netherlands was used to identify patients who developed an AR after a negative sentinel lymph node biopsy (SLNB) performed between 2002-2004. Using local hospital records we recorded primary patient-, tumor- and treatment characteristics, as well as salvage treatment.

Results: We identified 54 patients with an AR, median 30 months (range 3-79) after SLNB. Eighteen patients (33%) were initially treated with breast conserving therapy, 15 of whom received external beam radiation therapy (EBRT). Thirty-three patients (61%) did not receive adjuvant systemic treatment. In 45 of the 54 (83%) patients a salvage axillary lymph node dissection (ALND) was performed showing a median of 3 positive nodes (range 1-24). Nine patients (17%) were not treated surgically: 3 were treated with salvage EBRT and 6 with salvage systemic therapy only. At time of detection of the AR, a total of 7 patients (13%) had proven distant metastases. After a median follow up of 47 months (range 3-118) the 5-year "post-recurrence" distant metastasis free survival was 50% and overall survival was 58%. Significant negative predictors of survival were negative estrogen receptor (ER) status and receiving adjuvant chemotherapy at initial treatment.

Conclusion: AR following a negative SLNB is associated with a 58% 5-year OS. Prognostic factors are ER negative primary tumor and receiving adjuvant chemotherapy as a part of initial treatment, reflecting an aggressive phenotype. Adequate regional and systemic salvage therapy constitute a chance for long term survival after AR.

Keywords: Breast cancer, sentinel lymph node biopsy, axillary recurrence, loco-regional recurrence, prognosis

Introduction

Sentinel lymph node biopsy (SLNB) is the standard technique to stage the axilla in breast cancer patients with a clinically and ultrasound negative axilla. Meta analysis of the many registration trials on SLNB report a false negative rate of 5-7%[1,2] which led to the general acceptance of the technique. Only a minority of the falsly negative staged axillae develop overt axillary lymph node recurrence. Meta analysis of series with follow up results of patients with negative SLNB indicate a low axillary recurrence rate (ARR) of 0,3-0,6%[3-5]. This matches the results of randomized controlled trials in which equivalent overall survival (OS), disease free survival (DFS) and regional control have been found for completion ALND or no further treatment after a negative SLNB procedure[6,7]. The discrepancy between validation studies and the actual clinical ARR could be explained by tumor biology, postoperative radiotherapy and systemic adjuvant treatment regimens. Since the clinical ARR after SLNB is low only small numbers of patients with axillary recurrences (AR) have been reported, and therefore the prognosis and optimal salvage strategy is unclear.

The necessity of completion ALND after a positive SLNB, for at least a selected group of patients is currently under debate. The ACOSOG Z0011 trial enrolled patients with a T1-2 primary tumor treated by lumpectomy and external beam radiation therapy (EBRT) with a clinically negative but histologically positive SLNB. The study demonstrated equivalent OS and DFS for patients randomised to completion ALND or no further treatment[8,9].

If ALND will be omitted in an increasing number of SLNB positive patients, the number of patients with occult residual nodal disease will likely increase. The aim of the current study was to identify a large group of patients with an AR after negative SLNB and establish prognosis, as well as initial- and salvage treatment.

Materials and Methods

Patients

Through a retrospective analysis of the Dutch Cancer Registry of 16 breast cancer units we identified patients with AR after negative SLNB operated on between 2002-2004. Furthermore, the prospective databases of these hospitals were analyzed. All patients were treated according to contemporary Dutch breast cancer guidelines[10].

SLN-biopsy and pathology examination of lymph nodes

Visualization and identification of SLNs consisted of preoperative lymphoscintigraphy and intraoperative use of a γ-ray detection probe together with patent blue. Pathologic examination of SLNs was performed according to contemporary Dutch breast cancer guidelines[10]. SLNs were formalin-fixed, sliced into parts of 4 to 5 mm, embedded in paraffin and at least three cuts from the paraffin blocks were taken at 250-500 μm intervals. Sections were stained with haematoxylin and eosine (H&E) and immunohistochemically (IHC) with a keratin antibody. Tumor specimens were classified by size, type of tumor, malignancy grade and Estrogen- and Progesteron-receptor status (ER and PR). At the time HER2neu status was not routinely determined. The malignancy grade was determined using the modified Bloom and Richardson (BR) classification.

Adjuvant local and systemic treatment

Initial adjuvant systemic and/ or radiation treatment was given according to Dutch national breast cancer guidelines[10]. This is based on (axillary) lymph node status and primary tumor characteristics, sanctioned by the institutional multidisciplinary tumor board. Ultimately a shared decision making process with the patients and relatives determined the final treatment plan. During the study period neo-adjuvant therapy was considered a contra-indication for SLNB and therefore none of the patients in this study received neo-adjuvant therapy.

Follow-up

Follow-up was performed according to Dutch guidelines [10]. When no adjuvant treatment was given, patients were seen by a breast cancer specialist (surgeon, radiotherapist or medical oncologist) in the outpatient department every 6 months for 2 years, then yearly for up to 5 years. When adjuvant treatment was given patients were seen every 3 months for the first 2 years, thereafter biannually for 3 years. The visit included loco-regional clinical examination complemented by a yearly mammogram. Ultrasound of the axilla was not part of the regular follow-up regimen. The endpoints were distant metastasis and death.

Data collection

The Electronic Health Record Systems of all hospitals were used to indentify patient and tumor characteristics at time of the detection of the breast primary. The primary and adjuvant systemic treatment was documented.

The date of detection of the AR, whether patients were re-staged and subsequent local and systemic treatment were documented. In case of distant metastases the date of detection was noted. Follow up ended in august 2011. For patients still alive at this time, the date of the last outpatient clinic visit was considered last follow up.

Re-evaluation of initial systemic treatment

Since 2005, indications for adjuvant systemic treatment have evolved considerably. We therefore (re)considered the need for adjuvant systemic treatment according to current Dutch guidelines[11]. Patient-, tumor-, and surgical treatment characteristics were taken into consideration. The gain in DFS and overall survival of the hypothetical adjuvant treatment was computed using www.adjuvantonline.com[12].

Data-analysis

Kaplan-meier survival curves were calculated comparing survival for subgroups with different treatment of AR (ALND, radiotherapy, systemic therapy), different primary tumor characteristics (including hormone receptor status, size, BR grade and histology type), age, the number of positive nodes found on completion ALND and patients with an early versus late axillary recurrence (after two, and after three years).

Results

Patients

We identified 54 patients with AR after negative SLNB. Median primary tumor size was 19 mm (range 1-51). Bloom-Richardson Grade was II-III in 78% of all patients. A median of 1 (range 1-7) SLNs was harvested. Patient- and primary tumor characteristics are shown in table 1, as well as initial treatment. Three patients who underwent breast conserving therapy (BCT) did *not* receive whole breast irradiation. One patient who underwent mastectomy received EBRT. In total, therefore only 15 (28%) patients received whole breast irradiation. Twenty patients (37%) were treated with adjuvant systemic therapy, either hormonal or chemotherapy.

Table 1. Patient- tumor- and primary treatment characteristics

Axillary recurrence and salvage treatment

Median interval between SLNB and detection of the AR was 30 months (range 3-79). Almost all ARs (90%) were detected within 5 years of initial treatment. The majority of recurrences (25 patients) was detected between 24-42 months (46.3%).

Fifty patients (93%) were restaged demonstrating distant metastases in 7 patients. Salvage ALND was performed in 45 (83,3%) patients, identifying a median of 3 positive nodes (range: 1-24). More than 3 positive nodes were found in 19 patients (42%). The mean lymphnode ratio (LNR), previously shown to be predictive of prognosis in primary breast cancer[13], was 0.46. Twenty-eight patients (52%) received EBRT to the axilla and thoracic wall, 48 patients (89%) underwent adjuvant systemic therapy, 24 of these only endocrine therapy. Details on salvage treatment and restaging are shown in table 2 (details on adjuvant treatment was available for 52/54 patients).

Table 2. Treatment after axillary recurrence

Follow up post axillary recurrence

The median follow up post AR was 47 months (range 3-112). Nineteen additional patients developed distant metastases during follow up. Twenty-two (41%) patients died from metastatic disease during follow up.

Survival

Five-year DFS post recurrence was 50%, OS was 58%. Overall survival and distant disease free survival post-recurrence are shown in figure 1.

Overall survival was significantly worse in patients with an estrogen receptor negative (ER-) primary tumor (p=0.012), and for patients who received chemotherapy as part of their initial treatment (p=0.021) (figure 2). Survival was not significantly different for patients with different salvage treatment regimens, or with an early versus late recurrence (figure 3). DFS after AR was worse for patients who initially received chemotherapy (p=0.003).

Revision of adjuvant therapy

Comparing the indication for systemic adjuvant treatment in the 2002 guidelines with current guidelines, 30 patients would now be considered undertreated for their primary tumor. Eight patients would have been advised chemotherapy in addition to the endocrine treatment they received. Two patients treated with chemotherapy would have been advised additional endocrine treatment. Of 20 patients who did not receive any systemic treatment, 6 would have been advised chemotherapy and 5 endocrine therapy, 9 would have been advised both.

When entered in the Adjuvant!Online database these changes would have led to a median decrease of 4,6% (range 0,7-15,6) in mortality and a median increase of 13,8% (range 4,5-34,2) in relapse free survival.

Discussion

Since the widespread implementation of SLNB, little is known about the fate of the patients with an incidentally occurring clinical AR. Risk factors, treatment and eventual prognosis of the AR were the subject of a retrospective population based investigation.

We identified 54 patients with AR after negative SLNB, which is the largest series in the current literature. We demonstrate that these patients generally have a poor prognosis. In 14% synchronous distant metastases are present, 36% developed distant disease during follow up. Although the risk of AR after a negative SLNB procedure is low, impact on prognosis is significant, demonstrated by the 58% 5-year survival rate post recurrence. When compared to survival curves from the AJCC cancer staging manual, this is similar to stage IIIA (68%) or stage IIIC (49%) primary breast cancer, but better then stage IV (only 15% 5 year survival)[14].

The statistically significant predictors for overall survival were ER- status and receiving chemotherapy initially, both representing a more general unfavorable primary tumor biology in patients developing AR. Recent literature shows that constructed biologic subtypes are not only predictive of overall survival, but also of the chance of LRR[15]. It would therefore be interesting to know whether constructed subtypes would be predictive of survival in our series. Unfortunately Her2NEU status is unknown for 67% of our patients. It is therefore impossible to construct subtypes for our series.

This is the first study that specifically investigates patients with isolated axillary failure after N0(SLN) breast disease.

Anderson et al report on locoregional recurrence (LRR, other than ipsilateral breast) in node negative BCT patients participating in five different NSABP trials of adjuvant systemic treatment (after undergoing level 1 and 2 ALND)[16]. The 10-year LRR incidence was 1,9%, with 72,7% occurring within 5 years. LRR was associated with a poor prognosis; within five years after LRR 65,1% had died. Comparing these figures with the present report, the similarities regarding OS, time to recurrence and risk factors are striking. In this review too, prognosis was significantly worse for patients with ER- tumors. This suggests that irrespective of ALND, LRR is a harbinger of poor prognosis in a subset of patients with an aggressive tumor. Two important differences between this study and ours are the fact that the study also included nodal recurrences other than axillary nodes as well as

ipsilateral chestwall recurrences, and the fact that patients were already subjected to level 1 and 2 ALND. This might explain the even worse prognosis seen in this study.

Nearly 70% of our AR patients did not undergo whole breast irradiation at primary treatment. This can be attributed to the small proportion of BCT in the current group. Only 18 (33,3%) of the AR patients underwent BCT, three of whom without whole breast irradiation. In the same period, however, 67% of the pT1-2N0 patients in the Netherlands received BCT. The disproportional number not receiving whole breast irradiation in our series suggests that the omission of whole breast irradiation increases the risk of AR. This is in agreement with previous studies in which BCT with whole breast irradiation is associated with a lower ARR[5]. However, as is shown in table 1 patients undergoing BCT are also more likely to have a T1 tumor (72%) than patients undergoing mastectomy (42%).

Twenty patients (37%) received adjuvant systemic treatment of the primary tumor. This number would currently be much higher since the expanded indications for adjuvant systemic treatment. A Meta-analysis of published randomized trials has shown that adjuvant chemotherapy does indeed increase overall survival as well as decrease local- and regional recurrences[17]. Our re-evaluations of the indication for adjuvant systemic treatment using current guidelines indicated a theoretical decrease of 4,6% (range 0,7-15,6) in mortality and a increase of 13,8% (range 4,5-34,2) in DFS. Especially the predicted increase in DFS is indicative for the fact that systemic treatment helps to irradicate residual tumor in the axilla and therefore less patients will develop an AR.

We were unable to reproduce the results of earlier studies indicating a relation between the length of the disease free interval and the prognosis of patients with an AR[16,18]. This could be due to the relatively small number of patients in this study. It remains questionable whether early diagnosis of the AR would impact on prognosis .

This is a retrospective study and therefore could be subject to selection bias. Though the use of the National Cancer registry makes it unlikely that biopsy proven AR were missed, we have no information on patients presenting with disseminated disease as a first event, in whom no extensive search for AR was performed. Moreover, we do not have the exact number of patients with a negative SNB treated in the hospitals and therefore, the rate of AR could not be defined. Previous studies from our centers demonstrated that the AR rate was relatively high with 1.6 and 2.8 % respectively[19,20], but this is depending on the length of follow-up and

accuracy of registration of the recurrences. In a systemic review the estimated AR rate reported in the literature was 0.5%[5].

Given the low risk of AR after negative SLNB, a prospective study regarding this topic is unlikely to be performed. The small absolute numbers of patients with AR limit the search for reliable prognostic factors. Therefore higher level of evidence should be sought for in meta-analysis of randomized trials using the source data of these trials.

Increased efficacy of adjuvant systemic therapy, together with EBRT to the breast as part of BCT, is the basis for studies that randomize patients between ALND vs. no ALND in case of positive SLNB with favorable primary tumor characteristics. The Z0011 trial has already reported on equivalent survival and good regional control in a selected group of patients.[9,8] Despite these promising results in stage II breast cancer patients, this shift from extensive regional surgery towards SLNB and systemic treatment will increase the number of patients with occult residual tumor in the axilla after local therapy. Although adjuvant systemic therapy may be able to irradicate residual tumor in the axilla, an increase in the number of ARs can be expected.

Perhaps the most important question, is whether the AR is the actual cause of the poor prognosis, or an epiphenomenon in patients with an intrinsic worse prognosis. The latter would imply that an early detection of the AR (and treatment thereof) might result in better regional control, but not in an improved overall survival. This assumption is supported by previous studies concluding that an ipsilateral breast recurrence should also be considered a marker, rather than a cause of worse overall survival[21-23].

All but two patients underwent salvage ALND. A median of three involved nodes and a LNR of 0,46 show extensive regional disease burden. Therefore the majority of these patients must have either had undiagnosed extensive axillary involvement at primary presentation, or subsequent dissemination of the disease from one node to another. Both scenarios suggest aggressive regional treatment is indicated, including post ALND chest wall- and neck node irradiation.

Since the high risk of developing distant metastasis after AR, salvage "adjuvant" systemic treatment following regional salvage treatment seems indicated, provided re-staging does not already reveal synchronous metastatic foci. Results of the CALOR trial provide further guidance for the systemic treatment of these patients. This trial compared adjuvant systemic treatment versus no further treatment after radical surgery and radiotherapy in patients with a local- or regional recurrence. Overall survival as well as (secondary) disease free survival was

demonstrated to be significantly better for patients receiving chemotherapy [24].Even though the vast majority (87%) of patients included in this trial were diagnosed with a local recurrence rather than an lymph node recurrence, these results might support an aggressive systemic approach for patients with AR as well.

The combination of the poor prognosis after AR and the expected increase in incidence, emphasizes the need for more research on prevention and salvage treatment modalities.

Conclusion: AR following a negative SLNB is associated with a 58% 5-year OS. Prognostic factors are ER negative primary tumor and receiving adjuvant chemotherapy as a part of initial treatment, reflecting an aggressive phenotype of the primary tumor. Adequate regional and systemic salvage therapy constitute a chance for long term survival after AR. Adherence to (current) guidelines for systemic adjuvant therapy during initial treatment will likely decrease the number of axillary recurrences and improve prognosis.

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Ethical standards

This study complies with current Dutch law.

Disclosure / conflict of interest

The authors declare that they have no conflict of interest.

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