STUDY PROTOCOL

Project: Prognosis, prognostic factors and predictive factors in centimeter or subcentimeter node-negative breast cancer

Date: 140222

SPECIFIC AIMS

Because of mammography screening increasingly more women are diagnosed with centimeter or subcentimeter node-negative breast cancer (i.e., T1abN0); these tumors account for approximately 19% of all newly diagnosed breast cancers in Sweden. Although the long term relapse-free survival rates among patients with such tumors is as high as ≥90%, some reports suggest that certain patient subgroups may have rates <75%.[1] Firmly established prognostic and predictive factors for patients with T1abN0 tumors are, however, lacking. In Sweden, the treatment for T1abN0 tumors has changed over time and differs across health care regions with otherwise comparable health care systems. Leveraging these temporal and geographical differences, we propose to conduct a nationwide, register-based cohort study investigating long-term prognosis among patients with T1abN0 tumors. We aim to identify patient and tumor characteristics linked with poor prognosis, and to estimate the effect of adjuvant treatment on prognosis. Specifically, we will:

1. Estimate the risk of recurrence and survival among patients with T1abN0 tumors who have not received adjuvant systemic treatment.
2. Estimate the effect of radiotherapy versus no radiotherapy on risk of recurrence and survival among patients with T1abN0 tumors.
3. Estimate the effect of endocrine therapy versus no endocrine therapy on risk of recurrence and survival among patients with estrogen receptor (ER) positive T1abN0 tumors.
4. Estimate the effect of chemotherapy versus no chemotherapy on risk of recurrence and survival among patients with T1abN0 tumors.
5. Estimate the effect of trastuzumab versus no trastuzumab on risk of recurrence and survival among patients with human epidermal growth factor receptor 2 (HER2) positive T1abN0 tumors.

We will explore if the prognosis and treatment effects differ by age at diagnosis, whether the tumor was screening detected or not, type of surgery performed, tumor size (within T1abN0 tumors), tumor grade, ER-status or HER2-status. For comparison, we will run the abovementioned analyses among patients with node-positive T1ab tumors (i.e., T1abN1).

BACKGROUND

Sweden has experienced a substantial increase in both breast cancer incidence and breast cancer survival over the past decades. From 1980-2011, the age-standardized breast cancer incidence increased with >50%, from about 105 to about 160 per 100,000 person-years.[2] During the same period, the 10-year relative breast cancer survival increased from about 60% to >80%.[2] The remarkable increase in breast cancer survival is partly due to improvements in treatment, and partly due to proportionally more women being diagnosed with early breast cancer because of mammography screening. In 2012, 8,359 women were diagnosed with breast cancer in Sweden[3]; an estimated 1,588 (19%) had T1abN0 tumors.

As adjuvant treatment carries significant side effects, a major challenge is to tailor treatments based on prognosis without treatment, treatment benefit, and risk of side effects. This is a

clinical dilemma for patients with T1abN0 tumors because for this particular subgroup of breast cancer patients: 1) prognosis without adjuvant systemic treatment is not well characterized, 2) firmly established prognostic and/or predictive factors are lacking, and 3) the benefit of adjuvant systemic treatment is unclear. Each point is discussed briefly below.

Prognosis among patients with T1abN0 tumors
The precise prognosis among patients with T1abN0 tumors not receiving adjuvant systemic treatment is unclear. Most studies addressing this question are small, based on data from single institutions, include an unknown proportion of patients receiving adjuvant systemic treatment and differ in outcome measures (reviewed by Hanrahan[1]). Most studies also lack long-term (>10 years) follow-up; although breast cancer usually recur 2-3 years after diagnosis, recurrence can occur >10 years after diagnosis.[1] Notwithstanding these limitations, existing data suggest that patients with T1abN0 tumors have 10-15-year breast cancer survival rates ≥90%. For example, in one of the largest studies to date, Johansson et al. estimated the distant recurrence free survival among 538 women aged <60 years treated with surgery +/- radiotherapy (no adjuvant systemic treatment was recommended for these patients according to the regional treatment guidelines at that time) for T1abN0 cancer in 1986-1999 in south-east Sweden.[4] At 10 years, the distant recurrence free survival was 89.6% for women treated in 1986-1991 and 93.5% for women treated in 1992-1999. In another comparatively large study, Chia et al. studied 430 women treated with surgery +/- radiotherapy for T1abN0 tumors without vascular invasion in Canada in 1989-1991.[5] At 10 years, the breast cancer-specific survival was 92%. Similarly, in a re-analysis of the Swedish Two-County randomized trial of mammographic screening, the 15-year breast cancer-specific survival rate was ≥87% for all tumor grades among 495 patients with T1ab tumors (2.8% of T1a and 7.7% of T1b tumors were node-positive) who had not received adjuvant chemotherapy.[6]

Prognostic factors among patients with T1abN0 tumors
There are several established prognostic and/or predictive factors in overall breast cancer, including age at diagnosis, tumor size, nodal status, tumor grade, proliferation index, lymphovascular invasion, hormonal receptor status and HER2 status. The prognostic role of these factors has not been thoroughly investigated in T1abN0 tumors, however there are data indicating that they are important. According to some reports, women with high-grade T1abN0 tumors and/or T1abN0 tumors with lymphovascular invasion have 10-year relapse-free survival rates of <75%.[1,5] Likewise, results from several studies suggest that women who are young at diagnosis or who have HER2-positive or triple-negative T1abN0 tumors have a particularly poor prognosis.[1,7] (The predictive role of hormonal receptor status and HER2 status is also unclear[1,7], see also below.) Intriguingly, according to one study[8], patients with T1b (i.e., 0.6-≤1.0 cm) tumors with extensive lymph node involvement had a 40% reduced risk of breast cancer-specific mortality compared to patients with T1a (i.e., ≤0.5 cm) tumors with extensive lymph node involvement, suggesting that under certain circumstances smaller rather than larger tumors have poorer prognosis.

Taken together, existing data suggest that while patients with T1abN0 tumors as a whole have 10-15-year breast cancer survival rates ≥90%, certain subgroups of patients may have a considerably poorer prognosis.

Adjuvant treatment for overall breast cancer and for T1abN0 tumors
The most recent meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTG), an organization that brings together updated data on each woman randomized into all trials of the treatment of operable breast cancer, show that: 1) radiotherapy after breast-

conserving surgery reduces the 15-year breast cancer mortality by about one-sixth,[9] 2) contemporary polychemotherapy regimens reduce the 10-year breast cancer mortality with about one-third,[10] and 3) five years of tamoxifen for women with ER-positive tumors reduces the 15-year breast cancer mortality with about one-third.[11] Likewise, according to a 2012 Cochrane Review, adjuvant trastuzumab reduces overall mortality for patients HER2-positive disease with about one-third.[12] Importantly, the relative (and absolute) risk reductions of these therapies seem to independent of age at diagnosis, grade, stage and ER status, but the number of individuals with small cancers in these publications are few. This fact further enhances the importance of the present study. Furthermore, based on the differences over time and regional differences in adopting adjuvant therapies, we should be able to identify potential differences in outcome in relation to management.

Results from a few randomized trials and large observational studies indicate that adjuvant systemic treatment may have a benefit for patients with T1abN0 tumors. Only one randomized trial has been conducted exclusively for patients with T1abN0 tumors.[13] The trial included 1,009 patients and reported that the 8-year cumulative incidence of ipsilateral breast cancer recurrence was 16.5% with tamoxifen, 9.3% with radiotherapy and placebo, and 2.8% with radiotherapy and tamoxifen. Overall survival in all three groups was similar, 93-94%. Fisher et al. re-analyzed data from five clinical trials and included only women with T1abN0 tumors in the re-analyses.[14] Among 235 women with ER-negative tumors, the 8-year recurrence free survival was 81% after surgery alone and 90% after surgery and chemotherapy. Overall survival in the two groups was 93% and 91%, respectively. Among 1,024 women with ER-positive tumors, the 8-year recurrence free survival was 86% after surgery alone, 93% after surgery and tamoxifen and 95% after surgery, tamoxifen and chemotherapy. Overall survival in the three groups was 90%, 92%, and 97%, respectively. Finally, in the largest observational study to date, Hanrahan et al. interrogated the US Surveillance, Epidemiology, and End Results (SEER) Program data base.[15] Among 51,246 patients with T1abN0 tumors diagnosed in 1988-2001, among whom an unknown proportion received adjuvant systemic treatment, the 10-year breast cancer-specific mortality was estimated to be 4%, which is lower than expected had all patients been untreated.

Current clinical treatment guidelines
The weak evidence base for treatment of T1abN0 tumors is reflected in current clinical guidelines. According to the 2013 National Comprehensive Cancer Network (www.nccn.org) guidelines, adjuvant systemic treatment is not recommended for T1aN0 tumors. These guidelines also state that T1bN0 tumors may be divided into those with a low risk of recurrence, and those with unfavorable prognostic features (intramammary angiolymphatic invasion, high nuclear grade, high histologic grade, HER2-positive status, or hormone receptor-negative status) that warrant consideration of adjuvant therapy. The 2013 Swedish National Guidelines (www.swebcg.se), produced by the Swedish Breast Cancer Group (SweBCG), state that patients with T1abN0 tumors without other features indicating increased metastatic potential (e.g., vascular invasion) might not need adjuvant systemic therapy. If the tumor is, however, endocrine responsive, endocrine therapy should be considered. The Swedish guidelines make no distinction between T1aN0 and T1bN0 tumors.

STUDY PLAN AND PRELIMINARY RESULTS
We propose to conduct a nationwide, register-based cohort study with prospectively collected exposure and outcome information. The study cohort will be assembled using data from the six Swedish regional breast cancer registries (described in detail below), and will include women surgically treated for T1abN0/1M0 breast cancer. The cohort members will be followed for

outcome from 1976, when the first regional breast cancer registry was established, to 2012 or 2013 (depending on what data is available in the Swedish Causes of Death Registry). Women with a prior cancer diagnosis, except non-melanoma skin cancer and cancer in situ of the cervix, will be excluded from the cohort. The primary outcome is breast cancer specific mortality. Secondary outcomes are local recurrence, distant recurrence and overall mortality.

Description of the registries
Linkage between the registries outlined below will be performed using the national registration number, a unique personal identifier assigned to all Swedish citizens since 1947.

Each regional breast cancer registry prospectively compile data on patient characteristics, tumor characteristics, types of treatment (intended treatment, i.e., not treatment actually received) and follow-up (loco-regional and distant recurrence) for all newly diagnosed breast cancer cases in that region. A complete list of variables from the regional breast cancer registries that will be used for this study are described in Table 1. If needed, to validate the registry data and to collect data that is missing in the registries we will complement the registry data with data retrieved from the patients' medical charts through manual scrutiny. The regional breast cancer registries are continuously updated against the Swedish Cancer Registry and the Register of Population and Population Changes. The Swedish Cancer Registry was established in 1958 and obtains mandatory reported data from both clinicians and pathologists on all newly diagnosed malignant neoplasms. Information on the site and histopathological features of the tumors is recorded. The registry is estimated to be 96% complete.[16] The Register of Population and Population Changes contains the official Swedish population data, including dates of death and migration; the data have been available since 1960. Cause of death will be retrieved through a separate linkage to the Swedish Causes of Death Registry, available since 1961. Patients with breast cancer (ICD C50.0-C50.9) listed as the primary or secondary cause of death will be considered as a breast cancer-specific death.

The Stockholm-Gotland Regional Breast Cancer Registry
Year established: 1976.
Coverage: About 2.2 million inhabitants; about 23% of the Swedish population.
Introduction of a region-wide mammography screening program: 1986.
Treatment guidelines: Between 1977 and 1997, the regional guidelines stated that no adjuvant systemic treatment should be offered to patients with T1abN0 tumors except endocrine treatment for postmenopausal women with ER-positive tumors or unknown ER-status in selected cases or within randomized trials. After 1997, the guidelines state that all patients with ER-positive tumors or unknown ER-status should receive endocrine treatment. Since 2008, treatment has been offered in accordance with the national SweBCG guidelines (see above) with minor alterations. Radiotherapy has generally been offered to patients with T1abN0 tumors undergoing breast-conserving surgery since 1977.

The South-East Regional Breast Cancer Registry
Year established: 1982 (partial coverage), 1986 (full coverage).
Coverage: About 1.0 million inhabitants; about 11% of the Swedish population.
Introduction of a region-wide mammography screening program: 1986.
Treatment guidelines: Radiotherapy has been offered to patients with T1abN0 tumors undergoing breast-conserving surgery since 1982. No adjuvant systemic treatment has been offered to patients with T1abN0-tumors since 1982.

The North Regional Breast Cancer Registry

Year established: 1987.

Coverage: About 0.9 million inhabitants; about 9% of the Swedish population.

Introduction of a region-wide mammography screening program: Between 1988 and 1996 in different countries throughout the region.

Treatment guidelines: Since 1980, radiation therapy has been offered to all patients with T1abN0-tumors. Patients with ER-positive T1abN0 tumors with grade 1-2 have not been offered systemic adjuvant treatment, whereas patients with ER-positive T1abN0 tumors with grade 3 have been offered endocrine therapy since the 1980:ies. Patients with ER-negative T1abN0 tumors have been offered chemotherapy since the mid 1908:ies. Since the beginning of 2000:s, women with HER2-positive T1abN0 tumors have also been offered trastuzumab.

The Uppsala-Örebro Regional Breast Cancer Registry

Year established: September 1992.

Coverage: About 2.0 million inhabitants; about 21% of the Swedish population.

Introduction of a region-wide mammography screening program: Between 1978 and 1994 in different countries throughout the region.

Treatment guidelines: Adjuvant systemic therapy is not recommended routinely for tumors ≤ 10 mm, including no endocrine therapy for ER-positive tumors. Women ≤ 35 years have been recommended chemotherapy +/- Tamoxifen from 2003. Women with HER2-positive T1bN0-tumors have been recommended chemotherapy and trastuzumab from 2008. Radiotherapy after breast-conserving surgery has been recommended from 1980:ies but in some counties not implemented until 1994.

The South Regional Breast Cancer Registry

Year established: 1978.

Coverage: About 1.8 million inhabitants; about 19% of the Swedish population.

Introduction of a region-wide mammography screening program: 1987.

Treatment guidelines: Radiotherapy after breast-conserving surgery has been recommended sine 1978 except during some periods for some patients included in different studies. No adjuvant systemic treatment has been offered to patients with T1abN0-tumors except chemotherapy plus trastuzumab for HER2-positive T1bN0-tumors since 2010.

The West Regional Breast Cancer Registry

Year established: 1988.

Coverage: About 1.7 million inhabitants; about 18% of the Swedish population.

Introduction of a region-wide mammography screening program: Between 1988 and 1993 in different countries throughout the region.

Treatment guidelines: The 1989 regional guidelines states that no general recommendation for adjuvant systemic treatment can be given to women operated for lymph-node negative breast cancer, except endocrine therapy for postmenopausal breast cancer if the patient wishes treatment after discussion. According to the 1997 regional guidelines adjuvant systemic treatment should be offered to patients not included in clinical studies after discussion and if the tumor is node-positive or carries at least two of the following three risk factors: >2 cm in size, progesterone receptor negative and S-fas ≥12%. According to the 2007 regional guidelines patients with node-negative tumors <2 cm should be offered adjuvant systemic therapy (endocrine therapy, chemotherapy and/or trastuzumab, as appropriate) if the patient is <35 years of age or the tumor has at least one of the characteristics: triple-negative, HER2-positive or differentiation grade 2-3. Radiotherapy after breast-conserving surgery has been recommended since 1989.

CHARACTERISTIC (description)	INFORMATION AVAILABLE BY REGION*						
	Stockholm-Gotland	South	South-East	Uppsala-Örebro	West	North	National
Year registry started	1976	1978	1982/1986	1992	1988	1987	2008
Date of diagnosis (date)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age at diagnosis (years)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mode of detection (screening, not screening)	No	No	No	Yes	Yes	No	Yes
Menopausal status (premenopausal, postmenopausal)	Yes	No	No	Yes	Yes	No	Yes
Tumor side (left, right, bilateral)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Primary surgery performed (yes, no)	Yes	No	Yes	Yes	Yes	No	Yes
Hospital performing the surgical treatment (name of hospital)	Yes	Yes	Yes	Yes	Yes	No	Yes
Type of surgery performed (mastectomy, partial mastectomy)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Axillary lymph node dissection performed (yes, no)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sentinel node biopsy performed (yes, no)	2001-	Yes	Yes	No	2004-	No	Yes
Invasive cancer (yes, no)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-radical surgery (yes, no)	No	No	Yes	No	Yes	No	N0
Number of tumors (n)	Yes	No	Yes	No	Yes	No	Yes
Tumor size according to PAD (mm)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Number of nodes examined according to PAD (n)	Yes	No	Yes	Yes	Yes	Yes	Yes
Number of nodes positive for cancer according to PAD (n)	Yes	No	Yes	Yes	Yes	Yes	Yes
ER-status (negative, positive)	Yes	No	Yes	Yes	Yes	2000-	Yes
PR-status (negative, positive)	Yes	No	Yes	Yes	Yes	2000-	Yes
Elston grade (I, II, III)	2004-	No	Yes	Yes	1997-	Yes	Yes
HER2-status (positive, negative)	N0	No	2002-	2003-	2004-	2000-	Yes
Postoperative radiotherapy (yes, no)	Yes	No	Yes	Yes	X	X	Yes
Postoperative endocrine treatment (yes, no)	Yes	No	Yes	Yes	x	X	Yes
Postoperative chemotherapy (yes, no)	Yes	No	Yes	Yes	x	X	Yes
Preoperative chemotherapy (yes, no)	Yes	No	Yes	Yes	2004-	No	Yes

Statistical analysis

The cohort members will be followed from the date of breast cancer diagnosis to the date of breast cancer death (i.e., the primary outcome), emigration, death from other causes than breast cancer, or December 31, 2012 or 2013 (depending on data available), whichever occurs first. As a sensitivity analysis, women with metachronous breast cancer will be censored at the time of diagnosis of the metachronous tumor. In secondary analyses, loco-regional recurrence, distant recurrence, and death from any cause, respectively, will be considered the outcome. Survival rates will be estimated using the Kaplan-Meier method and statistical comparisons between relevant exposure groups will be conducted using the log-rank test. Cox proportional hazard regression will be used to calculate multivariable hazard ratios (HRs) and 95% confidence intervals (CI) of the association between relevant exposure groups and outcome. The primary exposure groups will be: 1) no adjuvant systemic treatment, 2) radiotherapy versus no radiotherapy, 3) endocrine therapy versus no endocrine therapy among patients with ER-positive disease (as defined by the treating institution at the time of treatment), 4) chemotherapy (any) versus no chemotherapy, and 5) trastuzumab versus no trastuzumab among patients with HER2-positive disease (as defined by the treating institution at the time of treatment). To explore if the prognosis or treatment effects differs by patient and/or tumor characteristics, we will run the above mentioned analyses separately in women based on age at diagnosis (<35, 35-<50, 50-<70, ≥70), if the tumor was screening detected (yes, no), node-positive (yes, no), tumor grade (Elston I, II, III), type of surgery performed (partial mastectomy, radical mastectomy), ER-status (negative, positive) and HER2-status (negative, positive), as appropriate. We will also explore if the prognosis or treatment effects have changed over time, differ by health care region, and/or differ by when mammography screening was introduced in a given health care region. Finally, we will estimate temporal trends in incidence of small breast tumors (T1abN0 and TabN1), how it varies by region, and if it has been influenced by the introduction of mammography screening and/or sentinel-node biopsy.

Preliminary data and power considerations

In a preliminary overview performed by SweBCG in 2012, the Stockholm-Gotland (n=4,373), North (n=1,515), South (n=1,367) and West (n=3,105) regional breast cancer registries included a total of 10,360 patients with T1abN0 tumors. The South-East regional registry included 2,726 patients with T1ab tumors, among an estimated 22% had node-positive disease. Thus, in total, an estimated 12,568 patients with T1abN0 tumors were available in these registries in the preliminary overview. With extended follow-up (follow-up ended between 2007 and 2010 for all registries in the preliminary overview), together with registry data from the Uppsala-Örebro region, which was not included in the preliminary overview, we estimate that at least 15,000 patients with T1abN0 tumors will be available for analyses in the study. Reliable estimates of breast cancer-specific mortality was not available in the preliminary overview, but 10-year overall mortality was about 15%. Presuming that the 10-year breast cancer-specific mortality is in line with the SEER data (4%)[15], we should have at least a total of 600 breast cancer-specific deaths and 2,250 deaths from any cause. This should provide sufficient power for the proposed analyses. For example, presuming a breast-cancer specific mortality of 5% among patients not receiving adjuvant systemic treatment, and that 25% of the patients received endocrine therapy or chemotherapy, the study will have a 80% power to detect a statistically significant (alpha-level: 5%) relative risk reduction of breast cancer-specific mortality of 22%. Presuming a breast-cancer specific mortality of 5% among patients not receiving adjuvant systemic treatment, that ER status is known for 60% (estimate based on the preliminary data) of the cases (n=9,000), that 85% are ER-positive (n=7,650), and that one-third of the patients with ER-positive disease received endocrine therapy, the study will have a 80% power to detect a statistically significant (alpha-level: 5%) relative risk reduction of breast

cancer-specific mortality of 28%. The study will have a higher power to detect differences in overall survival. It should be noted that for some of the proposed analyses data is scarce (e.g., HER2) and analyses will therefore be more explorative.

Limitations
The observational rather than experimental study design is a limitation of the proposed project. At least historically, year of diagnosis and region of residence rather than prognosis has been the main treatment determinants for patients with T1abN0 tumors in Sweden. Thus, bias stemming from the indication for treatment being related to prognosis (i.e., confounding by indication), one of the main reasons for conducting a randomized trial, should be minimized in this particular setting. Moreover, a corresponding randomized trial would require a very large study population followed for decades.

A second limitation of the proposed project is the lack of standardized ascertainment of exposure, covariate and outcome data over time and across health care regions. For example, the method used to determine tumor size, tumor grade, hormone receptor status and HER2 status has not been standardized. However, all relevant factors for this study have been used extensively in clinical practice and to our knowledge there is no reason to believe that any misclassification of these factors would be severe enough to invalidate the data. Moreover, one representative from each breast cancer registry will be involved in the analyses of the data and will be able to indicate if any data for a given registry for a given period is poor, including data on recurrence/follow-up. Thus, we should be able to address any major issues in the analyses phase of the project through running, for example, appropriate sensitivity analyses.

A third limitation is that the treatment data is based on what treatment was intended to be given to the patient (intention to treat), not what the patient actually received. This misclassification should presumably be non-differential with respect to outcome and could thus potentially bias the risk estimates towards null. On the other hand, the results will mimic the clinical setting where some patients stop adjuvant systemic treatment because of side effects.

SIGNIFICANCE
Yearly, in Sweden, an estimated 1,588 (based on 8,359 being diagnosed with breast cancer in Sweden in 2012 together with estimates from the Stockholm-Gotland region where 19% of women diagnosed with breast cancer 2011-2012 had T1abN0 tumors) women are diagnosed with T1abN0 tumors. Presuming that somewhere between 5% and 10% of these women will die from breast cancer, there are between 72 and 144 potentially preventable breast cancer deaths per year in Sweden alone. The proposed study, with an estimated 15,000 women with T1abNo tumors, will be the by far largest study to date with individual-level data on patient characteristics, tumor characteristics as well as treatment investigating prognostic and predictive factors among patients with T1abN0 tumors. Moreover, with up to more 35 years of follow-up for certain regions, this study will have a comparatively very long follow-up. This is potentially important as breast cancer can recur several decades after diagnosis. The proposed project thus holds promise to directly and indirectly impact breast cancer treatment and in the long run morbidity and mortality among patients with T1abN0 tumors. Directly by adding to the current evidence base for treatment of T1abN0 tumors, and indirectly by informing future clinical trials of adjuvant systemic treatment for T1abN0 tumors.

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