Impact of Management Changes on Loco-Regional Control of Breast Carcinoma: A 30-year Single Institution Experience Breast Cancer: Basic and Clinical Research

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Abstract

Purpose: This institutional-based study aims to reflect changes in diagnosis, surgery, radiotherapy, systemic therapy by retrospectively analysing treatment modalities and outcome during the past 30 years of breast cancer. We hypothesized these changes result in better outcome.

Material and methods: 2990 women are included, aged 18–95, no previous cancer, unilateral stage I-III primary breast tumors, breast-conserving surgery (BCS) or mastectomy (ME), postoperative radiotherapy (RT) and where indicated systemic treatment. Patients were divided in 3 cohorts stratified by year of diagnosis: 1984-1991, 1992-1999 and 2000-2008. The interval of cohorts was based on institutional changes in systemic regimens.

Results: Over time, median age at diagnosis was similar, patients >70 year increased (19.5 to 25.7%). Over the 3 cohorts: stage migration is observed, determination of tumor grading became routine, proportions of known ER/PR status increased. Over time an obvious shift to less mutilating surgery is observed. Systemic treatment increased significantly during the observed period.

In stage I disease, overall (OS), local control (LC) and disease free survival (DFS) didn’t change. In stage II, a significant increase in 10 years OS and DFS (p= 0.02 and 0.001) is observed. In stage III we noticed a significant increase in 10 years DFS (p=0.04) and trend in increase of 10 years OS (p= 0.06). Local Recurrence free survival (RFS) didn’t change significantly for all stages.

Conclusion: This study demonstrated an improved outcome for stage II and III over time in our population with the same local control. This is multifactorial, reflecting changes in diagnostic imaging, surgery and increased use of systemic therapy.

Keywords: Breast cancer; Long-term outcome; Management; Systemic treatment

Introduction

Breast cancer is the most common cancer among women and a leading cause of death worldwide, with in Belgium an incidence of 15% in 2012 [1]. Since 60’s local treatment transformed from radical mastectomies to current approach of breast-conserving therapy in early stages. Large prospective randomized trials [2-4] demonstrated similar survival rates after mastectomy and breast-conserving therapy followed by radiotherapy with same systemic therapy. Chemotherapy also changed, new products were developed: antracyclines and recently taxanes [5,6]. Biological data concerning Neu oncogene and hormone receptors became available. Over time women became better aware of the risk of breast cancer and participate more to screening mammography, which facilitated early diagnosis of smaller tumors [7]. Recently, there is growing interest in observational research with emphasis on understanding “real-world” outcomes of medical interventions. This population-based study aims to reflect changes in diagnosis, surgery, radiotherapy, chemotherapy and hormonal therapy by analyzing retrospectively the patient group, treatment modalities and outcome at our institution (UZ Brussel, VUB, Belgium) during the past 30 years. We hypothesized that these management changes result in better outcome.

Patients and Methods

Patient and tumor characteristics

This retrospective study, approved by University Hospital of Brussels’ ethics board (B.U.N. 143201421711) includes 2990 women, selected from UZ Brussel Radiation Oncology database according to following criteria: women aged 18–96, no previous diagnosis of cancer, unilateral invasive stage I-III primary breast tumors according to UICC TNM classification (2009), breast-conserving surgery (BCS) or mastectomy (ME) and postoperative radiotherapy (RT). Information was available regarding initial tumor characteristics, allocated treatment, first recurrence (distant or local) and dates last known alive or date and cause of death.

Patients were divided in 3 cohorts stratified by year of diagnosis: 1984-1991, 1992-1999 and 2000-2008. These intervals were based on institutional changes in systemic regimens. Patient-and tumor characteristics are shown in Table 1.

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most patients received (16.7%) 6 cycles of an antracyclines based scheme (5-fluorouracil, epirubicine, cyclophosphamide (FEC)). Since 2007 taxanes were routinely used for pN+ disease. Patients <65 years received 3-4 cycles of FEC followed by 12 weekly cycles of Paclitaxel [8]. Older patients were treated with Docetaxel and Cyclofosfamide [9].

Chemotherapy was given to 25.4% of patients in cohort1 and 39.7% in cohort 3 (Table 2). The first 2 cycles of FEC were given concomitant with radiotherapy.

Table 2: Treatment characteristics.
Results

Inter-cohort evaluation of patient and tumor characteristics

Over time, median age at diagnosis was similar for all cohorts, patients >70 year increased (19.5 to 25.7%) (Table 1).

Stage migration is observed: a 10% increase of stage 1 is noted, stage 2 decreased with same amount. Nevertheless the proportion of stage 3 stabilized.

Determination of grading and ER/PR status became routine, we noticed an increased proportion of grade 1 tumors.

Inter-cohort evaluation of treatment

Most patients (69%) in cohort 1 were treated with ME and AC. Over time an obvious shift to BCS and SN procedure is observed. In cohort 3 less patients underwent an AC.

Systemic treatment changed drastically during this period (1984–2008). Patients receiving chemotherapy increased significantly. In cohort 1 tamoxifen as hormonal treatment was used if Estrogen receptor (ER) was positive, irrespective of the Progesterone receptor (PR) status in cohort 1 and 2. Since 2008 high risk patients (T2, pN+, grade 3, PR negative, neu positive) were treated with an aromatase inhibitor. In total 72.7% of patients in cohort 3 received hormone therapy, tamoxifen or an aromatase inhibitor, with only 43% in cohort 1 being treated by tamoxifen, in correlation with hormonal receptors available at this period (half of patients were referred patients for radiotherapy).

Amplification of human epidermal growth factor receptor type 2 (Her 2 oncogene status) has been determined by immunohistochemistry and fluorescent in situ hybridization and trastuzumab (Herceptin®) becomes a standard of care in adjuvant setting since 1/6/2007.

Follow up

Follow-up was routinely performed with 3-6 monthly intervals, with annually bilateral or contralateral mammography’s, chest X-ray, liver ultrasound and bone scintigraphy during 5 years. Thereafter, clinical examination and bilateral or contralateral mammography was done annually.

Statistics

For statistical calculations computer software IBM SPSS 20° was used. Overall survival (OS), disease-free survival (DFS) and loco-regional control (LRC) were calculated from the day of diagnosis until time of death, relapse or last follow-up. The Kaplan–Meier method was used for estimation of survival rates. The level of significance was set at p ≤ 0.05.

| Stage I | Stage II | Stage III |
|---------|----------|-----------|
| 5 year | 10 year | 5 year | 10 year | 5 year | 10 year |
| Local recurrence free survival (%) | | | | | |
| Cohort 1 | 97.8 | 96 | 97.2 | 95.3 | 90.5 | 81.7 |
| Cohort 2 | 99.4 | 99 | 98.3 | 97.3 | 92.2 | 84.7 |
| Cohort 3 | 99.2 | 97 | 98.3 | 96 | 93.8 | 91.1 |
| p-value | | | | | | 0.111 0.487 0.6 |

Table 3: Local recurrence free survival (%).

Figure 1: Patient outcome vs. stage.
cohort 1 CMF was standard of care (12.8%), afterwards patients were preferentially treated with an anthracycline based scheme (16.7%), and since 2007 adjuvant taxanes were used routinely for node positive patients 1.1.

Determination of hormonal receptor status became a routine procedure and as a consequence hormonal treatment was more frequently used (cohort 1 vs. 3, respectively 43.2% and 72.7%) (Table 3).

Inter-cohort evaluation of patient outcome

In stage I disease, overall (OS) and disease free survival (DFS) didn't change over time.

In stage II, a significant increase in 10 years OS and 5 and 10 years DFS is observed. In stage III a significant increase in 10 years DFS and a trend in increase of 10 years OS is noticed (p-values: Figure 1).

Local Recurrence free survival (RFS) of about 2% did not change significantly for all stages during this period.

Discussion

This study focussed on changes in clinical presentation and therapeutic management over time in patients treated from 1984–2008 for breast carcinoma at a single institution. The goal of the study was to determine the effect of these changes on outcome.

Since 2001 the Belgian government organizes large media campaigns to aware women for the risk of breast cancer. Women aged 50–70 years are invited for screening mammography every 2 years. Since the beginning of screening, there has been a debate over benefit and harm and the balance between them [7]. Our results showed a stage migration with a 10% increase of stage I disease, while stage II decreased. We showed also an increased number of grade 1 tumors in cohort 3. These findings are similar with other studies [10,11]. Screening programs contribute to an increased diagnosis of stage I disease with favorable tumor characteristics, resulting in better overall and disease free survival, but at the cost of more anxiety and interventions [7]. The number of patients with stage III stabilized over time. An explanation could be that, although screening programs are available, there is only a partial participation (for example: 35.4% in 2003-2004 and 46.3% in 2007-2008 [12]). Participation depends on factors as socio-economic level and education [12]. Screening programs don’t reach all women and further awareness by government is necessary.

Although screening mammography is available since 2001 for patients aged between 50 and 70 years, the number of patients older than 70 increased in cohort 3. An explanation could be the increased life expectancy, with as consequence the higher risk to develop a tumor. Another reason could be the use of combined hormonal replacement therapy (CHRT) for menopausal symptoms. In 2002, the Women’s Health Initiative (WHI) showed an increase in invasive breast cancer and cardiovascular disease in a controlled trial of CHRT versus placebo [13]. In 2013, an integrated overview of the WHI findings [14] concluded from the intervention and post-stopping phases of WHI a 28% increased risk (95% CI, 1.11-1.48) of invasive breast cancer in women given CHRT.

For each patient, it’s important to define correct tumor stages. The past 30 years quality of imaging improved significantly allowing early detection of metastases: more patients were classified as stage IV disease. This 'stage migration', also called the 'Will Rogers phenomenon', can result in improved survival in both less and more severe disease stages [15]. We observed this in the SII to SI migration in our analysis over time even if the outcome in SI remains equal as well in SII and III, where better outcome is related mainly due to more appropriate systemic treatment.

In our institution, determination of hormonal receptor status became a routine procedure and as consequence, proportion of ER-positive patients increased significantly: respectively 42.2 and 45.8% in cohort 1 and 2 versus 77.1% in cohort 3. We observed the same for PR status. More patients received hormonal treatment (43% to 73%). Several studies demonstrated the impact of tamoxifen on 10–15 year survival improvement in women with ER/PR positive tumors [16,17]. In 2005, the first results of the BIG 1-98 and ATAC trial were published [18,19]. They showed that aromatase inhibitors (AIs), letrozole or and anastrozole, either as initial monotherapy or after 2 to 3 years of tamoxifen, significantly prolonged disease-free survival and time-to-recurrence. Additional follow-up will provide clearer information on long-term survival [20]. Since 2008, our high risk patients were treated with an AI. The increased use of hormone therapy contributed to increasing DFS and OS for stage II and III disease as reported in our study, although the difference in OS for stage III was not significant even after 10 years.

During this period, the use and schedules of systemic therapy increased both in adjuvant and preoperative setting. Nowadays the decision to use adjuvant chemotherapy takes several risk factors into account: stage, histopathology, such as expression of ER /PR receptors, HER 2 Neu status, and finally young age. These changes were based on several publications demonstrating that administration of adjuvant chemotherapy leads to significant reduction in risk of recurrence, breast cancer mortality and overall mortality. Anthracycline-based regimens are more effective than non-anthracycline-containing ones, adding taxanes improves DFS and OS in high-risk patients even more [5,6,21]. The increased use of anthracycline-containing chemotherapy in cohort 2–3 could have contributed to an improvement in DFS and OS for stage II and III. In our dataset the number of patients treated with taxanes is too small to show this extra survival benefit. Further follow-up of these patients is needed.

No difference in local recurrence in all stages over time is seen, although more women were treated by BCS. Many studies [2-4] published comparable long-term survival data after BCS or MA. A meta-analysis of 2011 by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)[3], reported the benefit of whole breast irradiation after BCS with a significant reduction in 10-year risk of recurrence by nearly half compared with BCS alone and a significant reduction in 15-year risk of breast cancer death. More recently, sentinel node (SN) biopsy has proven to be an appropriate alternative for axillary lymph node dissection in patients with early-stage and clinically node negative breast cancer. Several studies [22,23] showed a significant reduction of arm morbidity after SN procedure. The NSABP B-32 [24] trial demonstrated no significant differences in regional control, DFS and OS between patients treated with SN biopsy or axillary lymph node dissection with negative SN after a median follow-up of almost eight years.

Since January 2003, every file is discussed at multidisciplinary oncology meetings of the in-house Breast Cancer Oncology Group, which is comprised of all disciplines involved with diagnosis and treatment of breast cancer patients. This meeting provides also a forum to discuss and evaluate changes in standard of care. Previous review of adherence to consensus guidelines has revealed modest compliance in general [25]. Our institution, however, had significant success collaboratively ensuring changes in management of breast cancer...
patients. Several studies showed how improvement in adherence to guidelines resulted in an increase of dissected lymph nodes, better reporting of hormonal status and changes in dose intensity of chemotherapy.

Conclusion
This study demonstrated an improved outcome for stage II and III over time in our population. This improvement is multifactorial, reflecting changes in diagnostic imaging, surgery and increased use of hormone- and chemotherapy. Adherence to best practice guidelines and monitoring of treatment outcome data can realize further improvements. This study is limited by its retrospective design with inherent biases in patient and treatment modalities. The analysis provides population-based data from a large cohort of patients managed in an open access cancer care system with consistent treatment policies.

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Author Contributions
Conceived and designed the experiments: GM, MV, MDR, GS. Analysed the data: GM, MV. Wrote the first draft of the manuscript: GM, MV. Contributed to the writing of the manuscript: GM, MV, CF, MV, MDR, GS. Agree with manuscript results and conclusions: GM, MV, CF, MV, MDR, GS. Jointly developed the structure and arguments for the paper: GM, MV, GS. Made critical revisions and approved final version: GM, MV, CF, MV, MDR, GS. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics
As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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