Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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Part I

CHAPTER 1

General Introduction

Evolution of breast cancer treatment

Breast cancer is the most common female cancer, the second most common cause of cancer death in women (after lung cancer), and the main cause of death in women aged 45 to 55 years. In the Netherlands, the lifetime risk of developing breast cancer is 11% amongst women [1]. In the United States similar rates are reported. This translates into 11.500 new cases of breast cancer in the Netherlands and 211.240 new cases of breast cancer in the United States each year. In addition, 1 out of 20 to 25 women will die because of breast cancer [2].
Currently, overall survival rates for breast cancer are 80% after 5 years and 69% after 10 years of follow-up respectively [3].
Although mortality trends have been declining since 1992, the incidence of breast cancer in the Western World has risen since then, possibly due to the introduction of breast cancer screening programs. This means that although breast cancer treatment has improved over the past three decades, breast cancer still is a major subject of concern in terms of healthcare in our society [4].

Originally, treatment of breast cancer consisted of surgery alone and was aimed at aggressive locoregional eradication of tumor cells. In 1894 Halsted introduced the radical mastectomy in an era where breast cancer was normally treated by wide local excision alone which was associated with a high rate of locoregional recurrences [5]. The rationale of more aggressive locoregional therapy was based upon the hypothesis that more extensive resection would provide a better chance of disease control. The radical mastectomy implied “en bloc” removal of the breast, the overlying skin, both the pectoralis major and minor muscles, and the entire axillary contents (level I, II, and III nodes). The radical mastectomy resulted in a significant drop in local recurrence rates, and it became the standard of care for the treatment of breast cancer. However, despite the improvement in local control, the curative potential of this operation remained limited. In one series that followed 1438 women who had undergone radical mastectomy for 30 years, only 13 percent were free of disease, while 57 percent had died of breast cancer [6]. Therefore, in the 1970-ies, it was hypothesized that a less extensive operation, the modified radical mastectomy (MRM), could be performed without compromising survival. The term MRM implied complete removal of the breast tissue and the underlying fascia of the pectoralis major muscle, and removal of some but not all of the axillary nodes (levels I and II). Several prospective randomized trials documented equivalent survival rates with MRM as compared to radical mastectomy, with less morbidity [7-10]. These findings significantly changed the surgical approach to invasive breast cancer. More importantly, however, it supported the concept that breast cancer was not a local disease that spread contiguously, as Halsted proposed, but rather that systemic disease was ultimately the main determinant of survival. Variations in the treatment of local or regional disease were unlikely to affect survival.

While MRM was a less morbid procedure than radical mastectomy, it still required the loss of the breast. The question arose as to whether the breast could be preserved without compromising survival. Therefore breast-conserving therapy was introduced in the seventh and eighth decade of the twentieth century. Breast conserving therapy

refers to surgical removal of the tumor (with negative surgical margins) followed by radiotherapy to eradicate any residual disease. Six randomized clinical trials directly comparing breast conserving therapy with mastectomy and an overview of all completed trials have shown equivalent survival between the two treatment approaches although locoregional control rates after breast conserving therapy were significantly lower than after modified radical mastectomy [11-20].
In addition to changes in locoregional strategy of breast cancer treatment, the introduction of adjuvant polychemotherapy changed the concept of breast cancer treatment dramatically.
Over the past few decades, many randomized trials have been undertaken of various chemotherapy regiments for early breast cancer, and the data of these trials were included in quinquennial meta-analyses published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

This meta-analysis summarized results of every randomized trial that began before 1990 and involved treatment groups that differed only with respect to the chemotherapy regimens that were being compared. In 47 trials comparing combination chemotherapy with no chemotherapy, a significant reduction in mortality occurred in patients receiving chemotherapy irrespective of nodal status (negative vs. positive), estrogen receptor (ER) status (ER-rich vs. ER-unknown, or ER-poor), and whether or not hormonal therapy was administered. The benefit of chemotherapy, however, did vary substantially according to patient age and menopausal status. For all women younger than 50 years at randomization, combination chemotherapy improved 10-year survival from 71% to 78% for those with node-negative disease (an absolute benefit of 7%), and from 42% to 53% for those with node-positive disease (an absolute benefit of 11%). For women between 50 and 69 years at randomization, combination chemotherapy improved 10-year survival from 67% to 69% for those with node-negative disease (an absolute gain of 2%), and from 46% to 49% for those with node-positive disease (an absolute gain of 3%) [21, 22].

European Organization for Research and Treatment of Cancer

All studies presented in this thesis are derived from trials originated and conducted by the EORTC Breast Cancer Group. The work of this thesis has to a significant extent been performed during a fellowship at the Data Center of the European Organization for Research and Treatment of Cancer (EORTC) in Brussels, Belgium.

This organization was founded in 1962 by oncologists working in the main cancer research institutes of the EU countries and Switzerland. It was named Groupe Europe´en de Chimiothe´rapie Anticance´reuse (GECA), and became the European Organization for Research and Treatment of Cancer (EORTC) in 1968.

In 2004, group members entered a total of 4508 new patients in EORTC trials. An additional 971 patients from other research groups were treated as part of the intergroup study scheme managed by the EORTC Data Center, and in 2005 no less than 85 studies are open for entry and are being conducted by the EORTC Data Center.

The EORTC Breast Cancer Group is a multidisciplinary group involving surgeons, radiation oncologists and medical oncologists, pathologists, radiologists, biologists, psychologists and research fellows. Currently, the Group includes 17 institutions with the status of active member and 75 institutions with the status of probationary member. The main activity of the Group has been to carry out large clinical studies covering a wide spectrum of breast cancer patients. Translational research evaluating correlations between clinical outcomes and biologic tumor characteristics has become a high priority as well.
Examples of such investigations include studies presented in this thesis. Current activities include the potential predictive value of P53 gene mutation in primary chemotherapy of locally advanced breast cancer (EORTC 10994) and detection of micrometastasis in sentinel lymph nodes by PCR (EORTC 10981) and the role of radiotherapy after sentinel node biopsy in axillary node positive patients (AMAROS). Recently a hereditary task force addressing several aspects of hereditary breast cancer has been installed. This group is performing a large retrospective study on archival tumor in paraffin selected from 8000 patients previously treated in randomized EORTC trials, comparing treatment outcomes from patients carrying a proven BRCA 1 or 2 mutation or non-carriers.
The Group has prepared and is continuously updating the Manual for Clinical Research in Breast Cancer, used as a reference for protocol elaboration, data collection and reporting of results (recently also online: www.bco.org breast cancer online). This manual summarizes the major points in assessment, staging, treatment and follow-up of breast cancer patients. It enhances the uniformity of definitions and procedures in the various breast cancer protocols.
Within the last three years the number of patients included in clinical studies is stable: 1008 in 2002, 1020 in 2003 and in 2004 it was 856. A total of 9 clinical trials were open for the accrual in 2004.
Additionally, thousands of patients included in previous studies have been under continuous follow up in order to obtain long term results.

Rationale and aims of this thesis

In this thesis, several questions regarding specific issues both in locoregional treatment and in systemic treatment are evaluated. Therefore, the thesis is divided into three parts. Part I addresses questions concerning systemic treatment. Part II studies several aspects of locoregional treatment and outcome, and finally part III discusses the question whether specific tumor characteristics can discriminate very young patients with early stage breast cancer with a good outcome in terms of survival from similar patients who have a poor outcome.

Part I
Concerning adjuvant systemic polychemotherapy, the aspect of timing of administration of chemotherapy is studied. Experimental studies using murine models in the seventies and the eighties suggested that the administration of chemotherapy before or immediately after removal of the primary breast tumor resulted in a significant decrease in tumor cell proliferation in metastases and a

decrease in the upregulation of growth factors due to surgery [23-27].
Therefore, we tested the hypothesis that adjuvant chemotherapy given before or immediately after surgery improves disease outcome in terms of survival and locoregional control. In this thesis, two prospective studies conducted by the EORTC Breast Cancer Group are presented in which neoadjuvant and perioperative chemotherapy are evaluated.

EORTC trial 10854 studied the question whether or not chemotherapy given directly after surgery would yield better results in terms of locoregional control, disease-free survival and overall survival. Perioperative chemotherapy consisted of one short intensive course of fluorouracil, doxorubixin, and cyclophosphamide, administered within 36 hours after surgery. The eleven-year follow up results are presented in this thesis.

EORTC trial 10902 was conducted to study whether or not the administration of neoadjuvant chemotherapy in early breast cancer patients would lead to improved treatment outcome as well. This thesis reports the 5-year follow up results of EORTC trial 10902. The study group received 4 courses of fluorouracil, epirubicin, and cylclophosphamide, administrated before surgery. The control group received the same chemotherapeutic regimen given postoperatively.

Part II
As described above, breast-conserving surgery is similar effective in terms of long term outcome as compared to modified radical mastectomy but is associated with a higher locoregional recurrence rate [28]. The rationale for this finding can be explained by the fact that breast cancer is a systemic disease rather than a loco-regional disease. On the other hand, women who experience a locoregional recurrence have unfavorable prognosis and not surprisingly, a locoregional recurrence is a strong independent prognostic factor associated with unfavorable survival rates. Nevertheless, the general assumption is therefore that more aggressive surgery does not lead to better survival.

In relative contradiction with these findings are better survival rates described with subsequent adjuvant radiotherapy after modified radical mastectomy compared to modified radical mastectomy alone [29-32].

Therefore, we hypothesized that any improvement in long term outcome due to more aggressive locoregional treatment should be accompanied by an improvement in locoregional control.
Next, we hypothesized that a subset of patients can be identified that might benefit from more aggressive locoregional therapy at time of diagnosis to prevent an isolated locoregional recurrence. This subset consists of patients that developed a locoregional recurrence after primary treatment, received therapy and eventually developed systemic disease, but only after being disease-free for a long follow-up period. These are patients in which locoregional recurrence is an instigator rather than an associative factor for subsequent metastatic disease.

Therefore, we studied the question whether it is possible to identify patients in which

the prevention or successful treatment of locoregional recurrences could lead to better disease outcome. In addition, we studied the association between tumor characteristics and locoregional recurrence.

Part III
In the last part of this thesis, tumor characteristics of breast cancer in the very young breast cancer patient are studied. The prognostic impact of young age at onset is well known. However, the underlying pathophysiological mechanisms remain uncertain. Since patient age is a well-established risk factor associated with poor local control as well as unfavorable outcome in terms of survival [33-38], we studied the possibility to divide the very young patient group into a good- and a bad prognosis cohort. Next, we tried to gain further insight in chemotherapy responsiveness in hormone receptor positive- and hormone receptor negative young breast cancer patients groups since the effect of adjuvant systemic chemotherapy in the former group has been subject of discussion due to alternative treatment strategies and impaired chemosensitivity in this patient group [39-43].

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