Prognostication and treatment decision-making in early breast cancer

Fiets, Willem Edward

1

General introduction: Advances in prognosis and management of early breast cancer and outline of this thesis

ADVANCES IN PROGNOSIS AND MANAGEMENT OF EARLY BREAST CANCER

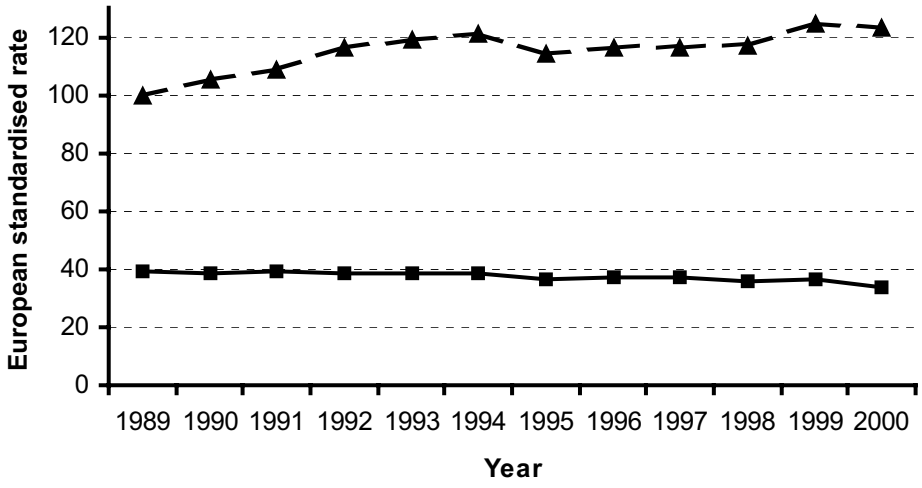
Breast cancer incidence and mortality

The incidence of breast cancer in The Netherlands is among the highest in the world. Breast cancer accounts for 33.6% of all cancers in Dutch women.[1] The absolute number of breast cancer cases increased from 7,900 in 1989 to 11,200 in 2000. In the same period the age standardised breast cancer incidence increased from 99.9 to 123.1 per 100,000 women (Figure 1). Based on present incidence rates, about 1 in every 8-9 women in The Netherlands will develop breast cancer.[1] Despite this increasing incidence, mortality due to breast cancer has slowly, but steadily, decreased from 39.0 per 100,000 women in 1989 to 33.5 in 2000 (Figure 1.1).[1] Between the 1970s and the early 2000s, the 5-year overall survival gradually increased from approximately 60% to approximately 80%.[2] The decrease in mortality has been attributed to the nationwide screening programme, which was gradually implemented in The Netherlands between 1989 and 1997.[3,4] However, evolvements in the management of early breast cancer, in particular the enhanced use of adjuvant systemic treatment, probably did have a greater impact on mortality.[5]

Primary treatment

Till 1980 primary surgical treatment of patients with early breast cancer consisted of modified radical mastectomy (MRM). In 1981 breast conserving therapy (BCT) was introduced in The Netherlands for patients with tumours ≤ 2 cm in diameter. In 1984 the indication for BCT was extended to tumours ≤ 3 cm. The proportion of patients receiving BCT gradually increased from 26% in 1984 to 53% in 1991.[6,7] Radiotherapy directed towards the whole breast, with an additional boost dose to

Figure 1.1. Annual, age-adjusted breast cancer incidence and mortality per 100.000 women between 1989 and 2000 *(Source: Netherlands Cancer Registry)*.



the original tumour site, was administered as part of BCT. Radiotherapy directed towards the thoracic wall and regional lymph nodes was given to almost all patients until the mid 1980s, but from that time the administration of locoregional radiotherapy was restricted to patients with a high risk for locoregional recurrence.[8] In the IKMN-region indications for locoregional radiotherapy were: tumour diameter more than 5 cm, irradical resection (axilla or thoracic wall), fixed axillary lymph nodes, more than 3 positive axillary lymph nodes, or a positive axillary top node.[9] The administration of locoregional radiotherapy in high-risk patients has a positive influence on survival. In the 1990s and early 2000s the primary management of early breast cancer remained largely unchanged, besides the introduction of the sentinel node biopsy procedure for staging the axilla in the late 1990s.

Adjuvant systemic therapy

In the 1980s and 1990s adjuvant systemic therapy was advised according to regional treatment guidelines. These guidelines recommended adjuvant systemic therapy for axillary node-positive (ANP) patients only. Chemotherapy was assigned to premenopausal ANP patients, and endocrine therapy to postmenopausal ANP patients (Table 1.1).[6,9] In premenopausal patients with ANP, oestrogen receptor (ER) positive tumours ovariectomy was considered equally effective as adjuvant chemotherapy,[10] but was generally not recommended. In the 1980s the proportion of ANP patients receiving any form of adjuvant systemic therapy increased from 49% in 1984 to 82% in 1991. The proportion of axillary node-negative (ANN) patients receiving adjuvant systemic therapy did not change and was less than 3%.[6] Between 1991 and 2000 the use of adjuvant systemic therapy remained stable,[4,5] but within The Netherlands differences in the management of ANN breast cancer grew.[11] Therefore, the Dutch Society for Medical Oncology organised in 1998 a consensus meeting on the adjuvant treatment of ANN breast cancer. Conclusions of this meeting were that adjuvant systemic treatment was indicated for all ANP patients, and for ANN

Table 1.1. 1996 IKMN-guideline for adjuvant systemic therapy.[9]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	any	any	any					
>0	any	any	any					

□ no adjuvant systemic therapy

■ adjuvant chemotherapy (4 cycles AC)

■ adjuvant endocrine therapy (tamoxifen for at least 2 years)

HR: hormone receptor; AC: doxorubicin / cyclophosphamide.

Table 1.2. 2002 Dutch guideline for adjuvant systemic therapy.[13]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	0.1-1.0	any	pos	■				
			neg	▪				
	1.1-3.0	I-II	pos	■				
			neg	▪				
		III	pos	■	■	■	▒	▒
			neg	▪	▪	▪	▪	
	>3.0	any	pos	■	■	■	▒	▒
			neg	▪	▪	▪	▪	
>0	any	any	pos	■	■	■	▒	▒
			neg	▪	▪	▪	▪	

□ no adjuvant systemic therapy

▪ adjuvant chemotherapy (4 cycles AC or 6 cycles CMF)

▒ adjuvant endocrine therapy (5 years tamoxifen)

■ adjuvant combination therapy (both modalities)

HR: hormone receptor; AC: doxorubicin / cyclophosphamide; CMF: cyclophosphamide / methotrexate / fluorouracil.

patients with a tumour diameter more than 3 cm, or with a tumour diameter between 1 and 3 cm and a poor histological grade or high mitotic counts.[11] The consensus was implemented in the multidisciplinary, evidence-based Dutch guideline for the treatment of breast cancer published in 2002 (Table 1.2),[12,13] and produced a 50% increase in the number of patients assigned to adjuvant systemic treatment.[14] In 2004 the 2002 guideline was revised. Indications for adjuvant systemic therapy were further extended (Table 1.3).[15]

Adjuvant endocrine therapy

In the 1980s adjuvant endocrine therapy with tamoxifen was recommended for patients with ER positive tumours only. But, between 1986 and 1991 the proportion of postmenopausal patients with ANP, ER negative tumours that received adjuvant tamoxifen increased from less than 10% to more than 40%,[6] a trend probably attributable to the results of some trials and meta-analyses reported in this period.[10,16,17] In line with this trend, the regional guideline from the Comprehensive Cancer Centre Middle Netherlands (IKMN), published in 1996, recommended tamoxifen for all ANP patients aged 50 years or more.[9] However, in 1998 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) concluded, based on their meta-analyses performed in1995, that in ER negative disease tamoxifen has little effect on recurrence or breast cancer related mortality.[18] On the other hand, in ER positive disease 5 years of treatment with tamoxifen reduces the breast cancer mortality rate by about 31%.[19] As a result, the 2002 Dutch guideline recommended that adjuvant tamoxifen should be given to patients with hormone receptor positive (oestrogen or progesterone) tumours only.[11-13] In recent years adjuvant treatment with aromatase inhibitors has emerged as a new, and probably more effective, option for postmenopausal patients with hormone receptor positive tumours.[20] In the ATAC trial, a trial comparing adjuvant treatment with anastrozole with adjuvant treatment with tamoxifen, anastrozole reduced the disease recurrence rate, by about 13%.[21] The 2004 Dutch guideline recommends an aromatase inhibitor after initial therapy with tamoxifen for all postmenopausal patients assigned to adjuvant endocrine therapy.[15]

Adjuvant chemotherapy

In the 1980s and early 1990s the preferred regimen of adjuvant chemotherapy comprised 6 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF).

Table 1.3. 2004 Dutch guideline for adjuvant systemic therapy.[15]

Number of positive nodes	Tumour size (cm)	Histological grade	HR	Age				
				<36	36-49	50-59	60-69	>=70
0	0.0-1.0	I	any					
		II-III	pos	■				
			neg	▪				
	1.1-2.0	I-II	pos	■				
			neg	▪				
		III	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	
	2.1-3.0	I	pos	■				
			neg	▪				
		II-III	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	
	>3.0	any	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	
1-3	any	any	pos	■	■	■	▪	▪
			neg	▪	▪	▪	▪	
>3	any	any	pos	■	■	■	■	▪
			neg	▪	▪	▪	▪	

□ no adjuvant systemic therapy

▪ adjuvant chemotherapy (5 cycles FEC or FAC, in specific patients 6 cycles TAC)

■ adjuvant endocrine therapy (premenopausal: 5 years tamoxifen; postmenopausal: tamoxifen for 2-3 years followed by an aromatase inhibitor for 3-2 years)

■ adjuvant combination therapy (both modalities)

HR: hormone receptor; FEC: fluorouracil / epirubicin / cyclophosphamide; FAC: fluorouracil / doxorubicin / cyclophosphamide; TAC: docetaxel / doxorubicin / cyclophosphamide.

In the 1990s this regimen was gradually replaced by a regimen comprising 4 cycles of doxorubicin and cyclophosphamide (AC). Although both regimens were considered equally effective[22] -both regimens reduce the annual breast cancer

mortality rate by about 27% among women aged under 50, and 11% among those aged 50-69[23]- AC was recommended instead of CMF, under the impression that AC was a lesser burden to the patient.[9] In 1998 the EBCTCG reported the suggestion that, compared to CMF, anthracycline-containing regimens produced somewhat greater effects on recurrence and mortality.[23] This suggestion was confirmed by their meta-analyses performed in 2000 (reported in 2005).[19] However, the anthracyclin-containing regimens tested were usually given for about 6 months, instead of 3 months with regular AC, and in combination with other cytotoxic drugs. Fluorouracil, doxorubicin, cyclophosphamide (FAC), and fluorouracil, epirubicin, cyclophosphamide (FEC) were the combinations most widely studied. Adjuvant treatment with FAC or FEC reduces the breast cancer mortality rate by about 38% among women aged under 50, and 20% among those aged 50-69.[19] The 2004 Dutch guideline for the treatment of breast cancer recommends adjuvant chemotherapy with a regimen comprising 5 cycles of FEC or FAC, instead of CMF or AC.[15] New, even more effective regimens are emerging. A recently published trial compared 6 cycles of treatment with either docetaxel, doxorubicin, cyclophosphamide (TAC) or FAC in women with axillary node positive breast cancer. In this trial treatment with TAC, as compared with FAC, resulted in a 28% reduction in the risk of disease recurrence.[24] Based on this trial, the 2004 Dutch guideline recommends TAC for premenopausal patients with ANP breast cancer overexpressing the HER2/neu receptor.[15]

OUTLINE OF THIS THESIS

As shown, in the past decades the management of early breast cancer has considerably changed. Adjuvant treatment decision-making has become much more complex, and prognostication has gained in importance. All studies in this thesis are dealing either with prognostication or with the consequences of a change in the management of early breast cancer.

Prognostic factors in early breast cancer are defined as measurements available at time of surgery that are associated with outcome. Prognostic factors are clinically relevant when they are used for treatment decision-making. In the 1980s involvement of the axillary lymph nodes was the only prognostic factor considered clinically relevant. The National Institutes of Health Consensus Panel on the Adjuvant Therapy and Endocrine therapy for Breast Cancer concluded in 1985 that routine administration of adjuvant systemic therapy in women with histological negative axillary lymph nodes could not be recommended.[25] But, in the late 1980s and early 1990s the administration of adjuvant systemic therapy to ANN patients became a mater of debate.[26,27] a major conclusion at the St. Gallen Conference held in 1988 was that most ANN patients should also be treated with some form of adjuvant therapy.[28] As a consequence, additional prognostic factors were needed to define high-risk ANN patients. For this matter, in 1989 a study was started in 5 hospitals located in the Middle-Netherlands. Consecutive patients with operable breast cancer were asked to participate in a prospective observational study on prognostic factors. The primary goal of this study was to evaluate the clinical relevance of a large number of potential prognostic factors. A secondary goal was to construct a prognostic index by which adjuvant therapy can be either omitted or adjusted to prognosis. This study is presented in **Chapter 2** of this thesis.

In studies on early breast cancer, outcome is usually defined as the time from diagnosis or surgery until a particular endpoint. The endpoint can vary, and may include death, disease related death, or recurrent disease. However, an explicit definition of the endpoint used is provided in less than half of published studies.[29] In **Chapter 3** data from the cohort of patients presented in Chapter 1 are used to evaluate the effects of various definitions of outcome on estimated outcome probability. The presented study specifically focuses on the influences of non-disease related death and contralateral breast cancer.

Hormone receptors are considered weak prognostic factors.[30] Three techniques for ER and progesterone receptor (PR) determination are commonly used: ligand binding assay (LBA), immunocytochemical assay (ICA), and enzyme immuno assay (EIA). At least until 1992, LBA has been the preferred and most commonly used method.[31] But nowadays, most, if not all, hospitals in the Netherlands use ICA. The prognostic value of EIA and ICA appear of the same magnitude compared with that of LBA.[32,33] But, the prognostic value of ICA and EIA has not been compared with each other before. In **Chapter 4** the prognostic value of ER and PR detected both by ICA and EIA is prospectively compared in a subgroup of patients from the cohort presented in Chapter 1.

The broad use of adjuvant systemic therapy in ANN breast cancer was introduced in the Netherlands after the 1998 consensus meeting. The Dutch guideline for the treatment of breast cancer, published in 2002, used tumour size, and histological grade or mitotic counts to select ANN patients for adjuvant systemic therapy.[12,13] In **Chapter 5** the reproducibility and prognostic value of histological grade and mitotic counts is studied specifically in patients with ANN breast cancer. Selected is a subgroup of patients from the cohort presented in Chapter 2, that is ANN and that did not receive adjuvant systemic therapy.

The major question, however, is not simply how to select patient categories that are at high risk for recurrence, but how to select patient categories for which the usefulness of adjuvant systemic therapy is high enough to justify its side effects and inconvenience. It is complex to predict the benefit of adjuvant systemic for an individual woman with early breast cancer. It involves integration of information about baseline prognosis, efficacy of various treatment options, and estimates of competing risk. In 2001 two computer programs, Adjuvant! and Numeracy, were introduced that provide an estimate of the absolute benefit associated with various commonly used regimens of adjuvant systemic therapy for the individual

woman with early breast cancer.[34,35] In **Chapter 6** the prognostic and predictive estimates made by Adjuvant! and Numeracy are mutually compared using the cohort of breast cancer patients presented in Chapter 2. In this chapter Adjuvant! is also validated for use in the Dutch setting. Prognosis determined with Adjuvant! is compared with the observed 10-year overall and relapse-free survival. In addition, the absolute benefit in overall survival from adjuvant systemic therapy as predicted by Adjuvant! is compared with the presence or absence of an indication for adjuvant systemic therapy according to the Dutch guideline from 2002 and the revised guideline from 2004.

For breast cancer patients, the optimal sequence of adjuvant chemotherapy and radiotherapy is not clearly defined. In the 1980s and 1990s both modalities were given concurrently in the IKMN-region. Theoretically, one can expect the largest treatment benefit with this policy.[36] However, it has been reported that the concurrent administration of the two modalities leads to an increased incidence of side effects.[37] In the 1990s adjuvant CMF chemotherapy was gradually replaced by adjuvant AC chemotherapy. In **Chapter 7** of this thesis the acute toxicity of radiotherapy alone, radiotherapy concurrent with AC, and radiotherapy concurrent with CMF is prospectively compared.

In **Chapter 8** the results and conclusions from the studies presented in this thesis are summarised and discussed in a broader perspective. **Chapter 9** is a translation in Dutch of this chapter.

REFERENCES

1. Visser O, Siesling J, van Dijck AAM, Editors. Incidence of cancer in the Netherlands 1999 /2000. Eleventh report of the Netherlands Cancer Registry. Netherlands Cancer Registry 2003. [available at: www.ikcnet.nl/bibliotheek].

2. Voogd AC, Coebergh JWW, van Oost FJ, de Vries E, Houterman S, van de Poll-Franse LV, Mols F. Kanker in Nederland. Trends, prognoses en implicaties voor zorgvraag. KWF Kankerbestrijding 2004. [available at: www.ikcnet.nl/bibliotheek]

3. Otto SJ, Fracheboud J, Looman CWN, Broeders MJM, Boer R, Hendriks JHCL, Verbeek ALM, de Koning HJ. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systemic review. Lancet 2003; 1411-1417.

4. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. Br J Cancer 2004; 91: 242-247.

5. Voogd AC, Coebergh JWW. Mortality reduction by breast cancer screening. Lancet 2003; 362: 245-246.

6. Voogd AC, van Beek MWPM, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JWW. Management of early breast cancer in southeast Netherlands since 1984. A population based study. Acta Oncologica 1994; 33: 753-757.

7. Hooning MJ, van Dongen JA, Went G. Changing indications for breast conserving therapy: proportion of patients with operable breast cancer suitable for breast conservation. Neth J Surg 1991; 28: 53-67.

8. Leer JWH, van de Velde CJH. Locoregionale radiotherapie na mastectomie niet voor alle Nederlandse borstkankerpatiënten zinvol. Ned Tijdschr Geneeskd 1999; 143: 73-75.

9. Oncologieboek IKMN: richtlijnen voor diagnostiek en behandeling van kanker voor medisch specialisten, huisartsen en paramedici in de IKMN-regio. Ed: Battermann JJ, van de Berg WN, Eliel MR. Utrecht: Intergraal Kankercentrum Midden-Nederland 1996.

10. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992; 339: 1-15.

11. Blijham GH. Adjuvante systeemtherapie voor kliernegatief mammacarcinoom. [available at www.nvmo.org].

12. Rutgers EJTh, Nortier JWR, Tuut MK, van Tienhoven G, Struikmans H, Bontenbal M, et al. CBO-richtlijn 'Behandeling van het mammacarcinoom'. Ned Tijdschr Geneeskd 2002;146:2144-2151.

13. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Richtlijn ‘Behandeling van het mammacarcinoom’. Utrecht: CBO; 2002.

14. Voogd AC, Louwman WJ, Coebergh JWW, Vreugdenhil G. Gevolgen op ziekenhuisniveau van de nieuwe richtlijnen voor adjuvante systemische behandeling bij mammacarcinoom. Ned Tijdschr Geneeskd 2000; 144: 1572-1574.

15. Anonymous. Herziening EBRO-richtlijn 'Behandeling van het mammacarcinoom'. Ned Tijdschr Geneeskd 2005;149:439.

16. Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. Adjuvant tamoxifen in the management of operable breast cancer. Lancet 1987; 2: 171-175.

17. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer: analysis at six years of Nolvadex Adjuvant Trial Organisation. Lancet 1985; 1: 836-840.

18. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. Lancet 1998; 351: 1451-1467.

19. Early Breast Cancer Trialists’ Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717.

20. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, et al. Use of Aromatase Inhibitors As Adjuvant Therapy for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Status Report 2004. J Clin Oncol 2005; 23: 619-629.

21. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005; 365: 60-2.

22. Fisher B, Brown AM, Dimotrov NV, Poisson R, Redmond C, Margolese RG, et al. Two Months of Doxorubicin-Cyclophosphamide With and Without Interval Reinduction Therapy Compared with Six Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-Node Breast Cancer Patients with Tamoxifen-Nonresponsive Tumors: Results from NSABP B-15. J Clin Oncol 1990 ;8:1483-1496.

23. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998; 352: 930-942.

24. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005; 352: 2302-2313.

25. NIH Consensus Conference: adjuvant therapy of breast cancer. JAMA 1985; 254: 3461-3463.

26. McGuire WL. Adjuvant therapy of node-negative breast cancer. N Eng J Med 1989; 320: 525-527.

27. DeVita Jr VT. Breast cancer therapy: exercising all our options. N Engl J Med 1989; 320: 527-529.

28. Glick HG. Meeting highlights: Adjuvant therapy for breast cancer. J Natl Cancer Instit 1988; 80: 471-475.

29. Altman DG, De Stavola BL, Love SB, Stepniewska KA. Review of survival analysis published in cancer journals. Br J Cancer 1995, 72, 511-518.

30. Pichon MF, Broet P, Magdelenat H, et al. Prognostic value of steroid receptors after long-term follow-up of 2257 operable breast cancers. Br J Cancer 1996; 73: 1545-1551.

31. Beex LVAM, Peterse JL, Nortier JWR, Veelen H van, Blankenstein MA. Receptoren voor steroidhormonen en mammacarcinoom. Ned Tijdschr Geneeskd 1992; 136: 2056-60.

32. Foekens JA, Portengen H, van Putten WLJ, Peters HA, Krijnen HLJM, Alexieva-Figusch J, Klijn JGM. Prognostic value of estrogen and progesterone receptors measured by enzyme immunoassays in human breast tumor cytosols. Cancer Res 1989; 49: 5823-5828.

33. Molino A, Micciolo R, Turazza M, et al. Prognostic significance of estrogen receptors in 405 primary breast cancers: A comparison of immunohistochemical and biochemical methods. Breast Cancer Res Treat 1997; 45: 241-249.

34. Loprinzi CL, Thomé SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. J Clin Oncol 2001; 19: 972-979.

35. Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19:980-991.

36. Kurtz JM. Can more breasts be saved if chemotherapy and radiotherapy are administered concomitantly? Ann Oncol 1999, 10, 1409-1411.

37. Kurtz JM, Miralbell R. Radiation therapy and breast conservation: cosmetic results and complications. Seminars in Radiation Oncology 1992, 2, 125-131.