Breast cancer

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Summary

Breast cancer is the most frequent female cancer in Europe and North America and poses an important health care problem. Over the last decades extensive literature has been compiled on the effectiveness of various diagnostic and treatment strategies, which has resulted in broad consensus on the most appropriate diagnostic and treatment strategies, laid down in clinical guidelines. The first chapters of this thesis assess breast cancer treatment in the North-Netherlands. The main objective of the studies presented in the chapters 1 to 5 is to obtain insight in the loco-regional treatment for early stage breast cancer, particularly the surgical treatment, including the axillary nodal staging, and adjuvant chemotherapy. In addition, in these studies the compliance with breast cancer treatment guidelines was evaluated. The aim of the studies in the second part of this thesis, comprising the chapters 6 and 7, is to asses the risk of second cancers after breast cancer. Emphasis in these studies lay on the influence of systemic and locoregional therapy on the risk of developing contralateral breast cancer and non-breast second cancers. In chapter 8 the first results of a project aiming to identify low penetrant breast cancer susceptibility genes in the North-Netherlands population are presented.

The literature concerning the evaluation of patterns of care and measuring the quality of care was reviewed in **chapter 1**. The review evaluates in more detail what aspects may determine the treatment of elderly breast cancer patients, the possible effects of a multidisciplinary approach of breast cancer treatment and the role of population-based cancer registries in the evaluation of breast cancer care in the present and in the near future.

In **chapter 2** we present an analysis of the variation in surgical treatment for early stage breast cancer and compliance with guidelines with respect to the application of radiotherapy and axillary lymph node dissection, before and after the introduction of the sentinel node biopsy in 13,532 stage I-IIIA breast cancer patients, diagnosed between 1989-2002. Large inter-hospital variation was observed in performing breast conserving surgery, which persisted after adjustment for case-mix. Generally, hospitals, which scored far under or above the regional average, did so during the whole study period. The guideline adherence with respect to axillary lymph node dissection and radiotherapy as part of breast conserving surgery was markedly lower for elderly patients and breast conserving therapy did not comply with guidelines in 25.2% of the patients aged 75 years or over. Guideline compliance fell since the introduction of the sentinel node biopsy procedure, from 96.1% prior to 2000 to 91.4% in 2002, frequently due to omission of axillary lymph node dissection or radiotherapy although indicated according to the guidelines. However, non-adherence to guidelines does not necessarily reflect poor quality of care. In our population, over the years 2001-2002, 50% of the patients without axillary lymph node dis-

section, most of which were older than 50 years, had a positive sentinel node biopsy. Radiotherapy, as part of breast conserving surgery, was more frequently omitted in the elderly patients, with 22% of the patients aged ≥75 years not receiving radiotherapy after breast conserving surgery. The benefit of axillary lymph node dissection for elderly patients has been questioned in the literature and surgeons may be reluctant to perform an additional axillary lymph node dissection (following breast conserving surgery or sentinel node biopsy) in elderly patients suffering from more serious co-morbidity. One could argue that the outcome of axillary lymph node dissection after a positive sentinel node biopsy would not often change the projected adjuvant treatment among elderly patients and as such may represent appropriate patient-tailored medical practice. A recent study by the Cancer and Leukaemia Group B, comparing lumpectomy plus tamoxifen with and without radiation in women with clinical stage I breast cancer aged ≥70 years, found only a small excess risk of locoregional recurrence in the non-irradiated group without differences in distant metastases risk or survival (Hughes et al, NEJM 2004;351:971-977). Local recurrences rates among elderly patients who refused radiotherapy or who had medical contraindications were found to be low for patients with small, lower grade tumors operated with adequate resection margins (Lee et al, Ann Surg Oncol 2004;11:316-321). Although inappropriate according to the guideline, omitting radiotherapy after breast conserving surgery in the very elderly therefore may also be adequate medical practice for patients with small, radically resected tumours.

The number of pathologically examined axillary nodes has been associated with breast cancer survival and examination of ≥10 nodes has been advocated for reliable axillary staging. In **chapter 3** the variation in the number of reported axillary lymph nodes and its effect on the axillary nodal stage were studied in 4,715 patients diagnosed between 1994-1997. The number of reported nodes varied between pathology laboratories, the median number of nodes ranged from 9 to 15 and between the individual hospitals. A decrease in the number of examined nodes was observed in older patients. A higher number of reported nodes was associated with a markedly increased chance of finding tumor positive nodes, especially more than 3 nodes. The frequency of node positivity increased from 28% if less than 6 nodes were examined to 54% if ≥20 nodes were examined, the percentage of tumors with ≥4 positive nodes increased from 4% to 31%.

The observed regional variation in axillary staging prompted a population-based study of the prognostic impact of a variable number of examined nodes, presented in **chapter 4**. Because age was previously found to be associated with the number of nodes examined, the prognostic effect of the number of nodes examined was also assessed using relative survival analysis. The crude survival was very similar for the entire patient population when comparing patients

with <10 and ≥10 examined nodes (81.5% versus 81.7%). But when analysis was performed with stratification for the number of positive nodes, crude survival was worse for patients with <10 examined nodes. When comparing the relative survival of patients with <10 and ≥10 examined nodes, adjusting for various patient and tumor characteristics, the relative survival was not found to differ. The prognostic effect of examining more lymph nodes appeared to largely reflect stage migration. The improved staging accuracy will result in a better prognosis in all patient strata, as defined in this study by the number of positive nodes, but will not affect the prognosis of the patient population as a whole. As we did not find an association between fewer pathologically examined nodes and relative survival, the association between fewer examined nodes and worse crude survival, observed in previous studies, can probably partly be explained by examination of fewer lymph nodes in the elderly patients. When evaluating disease outcome in elderly patients, competing causes of death should be accounted for, to prevent spurious associations of tumor characteristics with survival. On the other hand, the differences in relative survival associated with the number of nodes examined may have been too small to detect in our population. However, these differences are then likely very small. Another explanation for the absence of an association between relative survival and the number of examined nodes may be the relatively short follow-up in our study (median 5.6 years). It is possible that breast cancer deaths attributable to understaging patients, who were left wrongfully untreated, will become manifest only after longer follow-up.

In **chapter 5** we evaluated the administration of the 6 cycle CMF regimen among 251 consecutive axillary lymph node positive breast cancer patients <50 years, diagnosed between 1993 and 1996. The quality of CMF was measured using the interval between surgery and chemotherapy, the duration and dose of CMF chemotherapy and the resulting relative dose intensity (RDI) of CMF as indicators. The RDI was calculated as follows. Dose intensity was calculated by summarizing the administered dose of each drug over the number of courses (maximum 12 courses) and dividing this figure by the projected total dose of each drug over this number of courses, multiplying by the number of administered cycles and dividing by six (the projected number of cycles). The RDI follows from multiplying the arithmetical mean of the dose intensities for the three drugs with the ratio of the projected number of days for completion of the administered number of courses over the actual period of treatment. We found that only 94 patients (42%) completed adjuvant CMF without dose adjustment or delay. However, the overall median RDI was 92.6 (Inter Quartile Range 85.5-97.7) and 60 patients (24%) had a RDI <85. Myelotoxicity was the main reason for reductions and delays. Of 176 irradiated patients, 96% received radiotherapy simultaneously with CMF. Median CMF dose intensity nor median duration differed between patients who underwent mastectomy, mastectomy and radio-

therapy, or breast conserving therapy. Radiotherapy did not influence the median RDI. We concluded that the adherence to CMF treatment guidelines was generally good. Further, simultaneous radiotherapy did not affect the RDI of CMF. In **chapter 6** we assessed the risk of secondary invasive non-breast cancers in a recently treated population-based cohort of 42,563 breast cancer patients, focusing on the possible association with breast cancer treatment and the prognostic implications of secondary non-breast cancers. The cohort experienced 1.24-fold more secondary cancers than expected based on cancer incidence rates in the Dutch female population, or almost 15 extra cancers among 1,000 women each followed for 10 years. Cancers of the esophagus, colon, uterus, ovary, kidney, soft-tissue sarcomas, melanomas and acute myeloid leukemia all occurred more frequently than expected. Strikingly, there was a decreased risk of secondary non-breast cancers after chemotherapy when all sites were combined. Acute myeloid leukemia risk was borderline significantly increased (Hazard Rate 2.69; 95% Confidence Interval 0.99-7.26). Hormonal therapy increased endometrial cancer risk 1.9 fold among patients ≥50 years. The risk of soft tissue sarcomas was borderline significantly increased after radiotherapy (Hazard Rate 2.56, 95% Confidence Interval 0.98-6.65). The occurrence of secondary non-breast cancers did markedly worsen the patient's prognosis (Hazard Rate 3.76, 95% Confidence Interval 3.53-4.01). We concluded that our results, covering a 10-year follow-up period, did not indicate that the issue of treatment-induced secondary non-breast cancers has important implications for contemporary treatment strategies, since for most secondary non-breast cancers the association with previous treatment, if present at all, was weak. The results of a study on the impact of age and adjuvant therapy on contralateral invasive breast cancer risk and the prognostic significance of contralateral breast cancer are described in **chapter 7**. The study included 33,930 surgically treated stage I-IIIA breast cancer patients diagnosed in the Netherlands between 1988-2000. A total of 476 contralateral cancers were diagnosed <6 months (synchronous) and 999 ≥6 months (metachronous) after the index cancer. Older age and lobular histology were found associated with an increased risk of synchronous contralateral cancer. The Standardized Incidence Ratio, the observed number of contralateral cancers divided by the number of breast cancers expected if these patients would have had the same incidence as the general Dutch female population, decreased with age for metachronous contralateral cancer. The Standardized Incidence Ratio was13.4 (95% Confidence Interval 9.6-18.2) for women aged <35 and 1.6 (95% Confidence Interval 1.4-1.8) for women aged ≥60 years. The cohort experienced almost 30 extra cancers among 1000 women, each followed for 10 years, patients <35 years even experienced more than 70 extra cancers among 1000 women, each followed for 10 years. The cumulative risk of metachronous contralateral breast cancer increased with about 0.5% per year, reaching 5.3% after 10 years. A Cox Proportional Hazards analysis showed that

adjuvant hormonal therapy (Hazard Ratio 0.54; 95% Confidence Interval 0.44-0.68) and chemotherapy (Hazard Ratio 0.67; 95% Confidence Interval 0.51-0.87) considerably decreased the risk of metachronous contralateral cancer. The effect of radiotherapy differed markedly according to age at diagnosis of the index cancer. Whereas no excess risk of metachronous contralateral cancer was seen among patient aged ≥40 years, among patients <40 years radiotherapy was associated with a 1.6-fold (95% Confidence Interval 1.01-2.53) increased risk. The survival of patients with metachronous contralateral breast cancer was worse than for unilateral breast cancer patients. This study showed that young breast cancer patients experience a very high risk of synchronous and metachronous contralateral cancer and that adjuvant hormonal as well as chemotherapy considerably reduced the risk of contralateral cancer. As no decrease in risk over time was observed and metachronous contralateral breast cancer negatively affects the patient's prognosis, long-term screening of the contralateral breast at regular intervals remains necessary.

The study presented in **chapter 8** assessed the association of breast cancer risk and putative genes within the HLA region. Using germline DNA, the HLA region of 956 breast cancer patients and 1,271 family-based controls was genotyped with 24 microsatellite markers and markers for two Single Nucleotide Polymorphisms (SNPs) in TNFalpha and TNFbeta. With association analyses and the haplotype sharing statistic we evaluated the HLA region for differences in haplotype sharing between patients and controls. The haplotype sharing statistic showed a significant difference between patients and controls for four consecutive markers (D6S2671, TNFa, D6S2672 and MICA), the highest being at D6S2671 ($p = 0.017$). For subgroup analysis, patients were divided, based on (familial) breast cancer risk profile, into a high, moderate and low risk group. Intermediate risk patients were patients with either bilateral breast cancer, breast cancer before age 45, or two relatives with breast cancers, at least one of which had her breast cancer diagnosed before age 60. High risk patients fulfilled any of the moderate risk criteria and had a positive family history of ovarian cancer or male breast cancer, had breast cancer before age 35 or two relative with breast cancers, at least one of which had breast cancer diagnosed before age 45 and the other before age 60. The subgroup analyses showed that moderate-risk patients were responsible for the difference in mean haplotype sharing, with the strongest association for D6S2672 ($p = 0.0009$). A single haplotype was more frequent in moderate-risk patients than in controls. The results were confirmed with association analyses. Individuals homozygous for haplotype 110-184 (D6S2672-MICA) were observed in 9.0% of moderate-risk patients and 1.5% of controls [odds ratio (OR)=7.14], while heterozygotes were at a lower risk (OR=1.41), suggesting a recessive effect. The results revealed a potential role of the HLA class III sub region in susceptibility to breast cancer in patients at moderate familial risk.