Prognostication and treatment decision-making in early breast cancer

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The effects of non-breast cancer related death and contralateral breast cancer on estimated outcome probability in patients with early breast cancer.

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ABSTRACT

Background: A wide variation of definitions of recurrent disease and survival are used in the analyses of outcome of patients with early breast cancer. Explicit definitions with details both on endpoints and censoring are provided in less than half of published studies.

Methods: We evaluated the effects of various definitions of survival and recurrent disease on estimated outcome in a cohort of 463 patients with primary breast cancer. Outcome estimates were determined both by the Kaplan-Meier method and by a competing risk method.

Results: The in- or exclusion of contralateral breast cancer or non-disease related death in the definition of recurrent disease or survival strongly affected estimated outcome probability. The magnitude was dependent on patient-, tumour-, and treatment characteristics. Minor differences were observed between estimated outcome determined by the Kaplan-Meier method and the competing risk method.

Conclusions: Insight in the contribution of non-disease related death or contralateral breast cancer to estimated recurrent disease rate or overall death rate is indispensable for a correct interpretation and comparison of outcome analyses.

INTRODUCTION

In studies on early breast cancer, outcome is usually defined as the time from diagnosis or surgery until a particular event of interest (endpoint). The event of interest can vary and may include death (overall survival), disease related death (disease specific survival), or recurrent disease (disease free survival).

Altman et al. systematically reviewed the appropriateness of the application and presentation of survival analysis in clinical oncology journals.[1] They found that among papers specifically dealing with death as an end-point, only 47% explicitly described this end-point as either any death or only cancer-related death. In as much as 61% of papers that studied time to progressive disease the handling of non-cancer related mortality was not clearly defined.

In studies on patients with early breast cancer a wide variation of definitions of disease free survival is used. These definitions always include local recurrence, regional recurrence, and distant metastasis, but sometimes also include non-disease related death, contralateral breast cancer and in some cases second primary cancer. For example, the 1998 overview of randomised trials on adjuvant therapy includes contralateral breast cancer in the analysis of disease recurrence, but does not include non-disease related death.[2] The Intergroup includes non-disease related death, but contralateral breast cancer only when it occurs concurrently with a locoregional or distant relapse.[3] In the original reports of the NSABP B14 and B20 trials both non-disease related death, contralateral breast cancer, and second primary cancer were included as events in the definition of disease free survival.[4,5] In a recent report with long-term findings from these trials the definition of recurrence free survival was restricted to local or regional recurrence, or distant metastasis.[6]

Despite these different definitions, many papers on breast cancer survival do not provide an explicit definition of recurrent disease. Mirza et al. wrote a review on prognostic factors in node-negative breast cancer.[7] In the methods section of their report they stated that only papers in which overall or disease free survival were specified were included in their review. Sixty-three papers from their reference list dealt with survival analysis in primary breast cancer. We reviewed the definitions of recurrent disease used in these 63 papers. In only 21 out of 47 papers that studied time to recurrent disease the definition of recurrent disease explicitly described the handling of non-cancer related mortality. Intercurrent deaths were censored in 14 papers and counted as events in 7 papers. Eight papers explicitly described the handling of contralateral breast cancer. Contralateral breast cancer was censored in 1 and considered as event in 7 papers. The handling of second primary cancer was described in 7 papers. Second primary cancer was censored in 2 and counted as event in 5 papers.

In most papers the survival probability is estimated with the Kaplan-Meier method from observed survival times, censored or uncensored.[8] Censoring may arise due to end of follow-up, loss to follow-up, but also due to a competing event that makes further follow-up impossible. The Kaplan-Meier method requires non-informative censoring, which means that those individuals who are censored should be as likely to have the subsequent event of interest as those who remain in the study. In particular competing events might cause informative censoring. For this reason others have propagated an approach that accounts for informative censoring in survival analyses in the presence of competing events.[9,10,11]

In the present study we used data from a cohort of 463 patients with primary breast cancer to evaluate the effects of various definitions of survival and relapse on estimated survival probability. We specifically focused on the influences of non-disease related death and contralateral breast cancer. A second goal was to

evaluate whether differences could be assessed in estimated outcome determined either by the Kaplan-Meier method or a competing risk method.

Table 3.1. Patient-, tumour-, and treatment characteristics

	Number of patients (%)
Age	
≤ 50 year	142 (31)
51-70 year	213 (46)
>70 year	108 (23)
Primary surgical therapy	
Breast conserving therapy	266 (57)
Modified radical mastectomy	190 (41)
Other	7 (2)
Adjuvant systemic therapy	
Hormonal therapy	142 (31)
Chemotherapy	72 (16)
Histology	
Ductal	290 (63)
Other	173 (37)
Tumour size	
≤ 20 mm	272 (59)
> 20 mm	191 (41)
Axillary lymph nodes	
Negative	278 (60)
Positive	185 (40)

MATERIAL AND METHODS

Between October 1989 and March 1993 463 patients diagnosed with operable, stage I to III breast cancer agreed to participate in a prospective registration study on prognostic factors. We obtained written informed consent from all patients. Treatment was given according to the guidelines of the Comprehensive Cancer Centre Middle Netherlands. Patient-, tumour- and treatment characteristics are shown in Table 3.1. We assessed follow-up data until December 2002.

The events that were used to determine the different definitions of outcome were local- and regional recurrent disease, contralateral breast cancer, distant metastasis, disease related death and non-disease related death. In the various analyses these events were either ignored, considered as event of interest or as competing event (censored), depending on the definition of outcome. Definitions of overall survival, diseases specific survival, disease free interval, and disease free survival are given in Table 3.2. We defined local recurrent disease as either recurrence in the skin or soft tissue of the chest wall or in the ipsilateral breast. Regional recurrent disease confined recurrence in the lymph nodes in the ipsilateral axilla, the infraclavicular fossa or the internal mammary chain. Contralateral breast cancer included invasive breast cancer lesions in the contralateral breast regardless of histological type, lymph node involvement, and time interval from initial therapy or from subsequent recurrent disease. Breast cancer lesions at any other site, including the ipsilateral supraclavicular lymph nodes, were classified as distant metastases. We classified death as disease related when death was probably caused by breast cancer in the presence of distant metastases. Otherwise we classified death as non-disease related.

Survival probabilities were determined both by Kaplan-Meier estimates,[8] and cumulative incidence competing risk analyses. As outlined by others, the competing risk analyses were determined in a two-step process.[9,10] First we

Table 3.2. Definitions of outcome.

Overall survival	Time from surgery until death from any cause
Disease specific survival	Time from surgery until death related to breast cancer. Death not related to breast cancer is censored (Kaplan-Meier analysis) or treated as competing event (competing risk analysis).
Disease free interval	Time from surgery until recurrent disease*. Death not related to breast cancer is censored (Kaplan-Meier analysis) or treated as competing event (competing risk analysis).
Disease free survival	Time from surgery until recurrent disease* or death from any cause.

In the definition of recurrent disease local recurrence, regional recurrence, and distant metastasis are considered events; contralateral breast cancer is ignored, treated as event or censored (Kaplan-Meier analysis) / treated as competing event (competing risk analysis).

determined outcome estimates with the Kaplan-Meier method considering both the events of interest and the competing risk events as 'events'. In the second step, we calculated the conditional probabilities of experiencing the event of interest. With these probabilities we estimated the cumulative incidences in the event of interest.

RESULTS

During median 10.0 years of follow-up 149 patients died. 91 deaths were related to breast cancer, and the other 58 patients died from causes unrelated to breast cancer. Local recurrences were diagnosed in 28 patients, regional recurrences in 24. Distant metastases occurred in 111 patients, and in 30 patients breast cancer was diagnosed in the contralateral breast.

Table 3.3. Estimated 10-year survival rate according to definition of survival determined both by Kaplan-Meier method and the competing risk analysis.

| Survival definition	10-year survival rate (%)					
	all patients		no adjuvant systemic therapy		adjuvant systemic therapy	
	KM	CR	KM	CR	KM	CR
Overall survival	68.0	68.0	75.8	75.8	58.6	58.6
Disease specific survival	79.3	80.6	85.3	86.2	71.9	73.7
Disease free survival						
contralateral ignored	59.3	59.3	65.8	65.8	51.2	51.2
contralateral censored	58.6	59.4	64.9	66.0	51.1	51.6
contralateral event	55.5	55.5	59.9	59.9	50.2	50.2
Disease free interval						
contralateral ignored	69.4	70.9	74.6	75.8	63.0	64.9
contralateral censored	68.9	70.9	73.9	75.9	63.2	65.4
contralateral event	64.8	66.5	67.6	69.2	61.3	63.4

KM: Kaplan-Meier method; CR: competing risk analysis.

Estimated with the Kaplan-Meier method, after 10 years of follow-up 68% of patients were still alive (overall survival). If no one had died from causes other than breast cancer, 79% of patients would have been alive (disease-specific survival) (Table 3.3). The estimated 10-year risk of recurrent disease varied between 31% and 44% depending only on the definition of relapse. After 10 years of follow-up 56% to 59% of patients were still alive and free of recurrent disease (disease free survival), but if no one had died in the interim period 65% to 69% of patients would have been free of recurrent disease (disease free interval) (Table 3.3). Compared with the competing risk approach, the Kaplan-Meier method slightly underestimated 10-year survival rates when one or more competing events were censored instead of ignored. The largest difference (2.0 percent-point) was found when both non-disease related death and contralateral breast cancer were censored (Table 3.3).

Non-disease related death

The difference in estimated survival probability between overall survival and disease related survival, and between disease free survival and disease free interval is by definition caused by the handling of non-disease related death. As older age is associated with a higher probability of non-disease related death, we evaluated the effect of patient's age on estimated survival probability using the various definitions of survival. As shown in table 4, patients aged more than 70 years were at risk for dying from a cause unrelated to breast cancer, whereas patients aged 50 years or less seldom died from a cause unrelated to breast cancer. As a consequence, in the younger subgroup 10-year overall survival was almost equal to 10-year disease specific survival. Whereas in the elderly, estimated 10-year disease specific survival was more than 30 percent point better than estimated 10-year overall survival (Figure 3.1). In the younger subgroups differences between Kaplan-Meier and competing risk estimates were limited (≤ 1%). In the elderly estimations of 10-year disease specific survival were 82.2%

Figure 3.1. Influence of survival definitions on estimated outcome probability in breast cancer patients 50 years or less of age (A), and over 70 years of age (B). Both by Kaplan-Meier method (solid line) and competing risk analysis (dotted line).
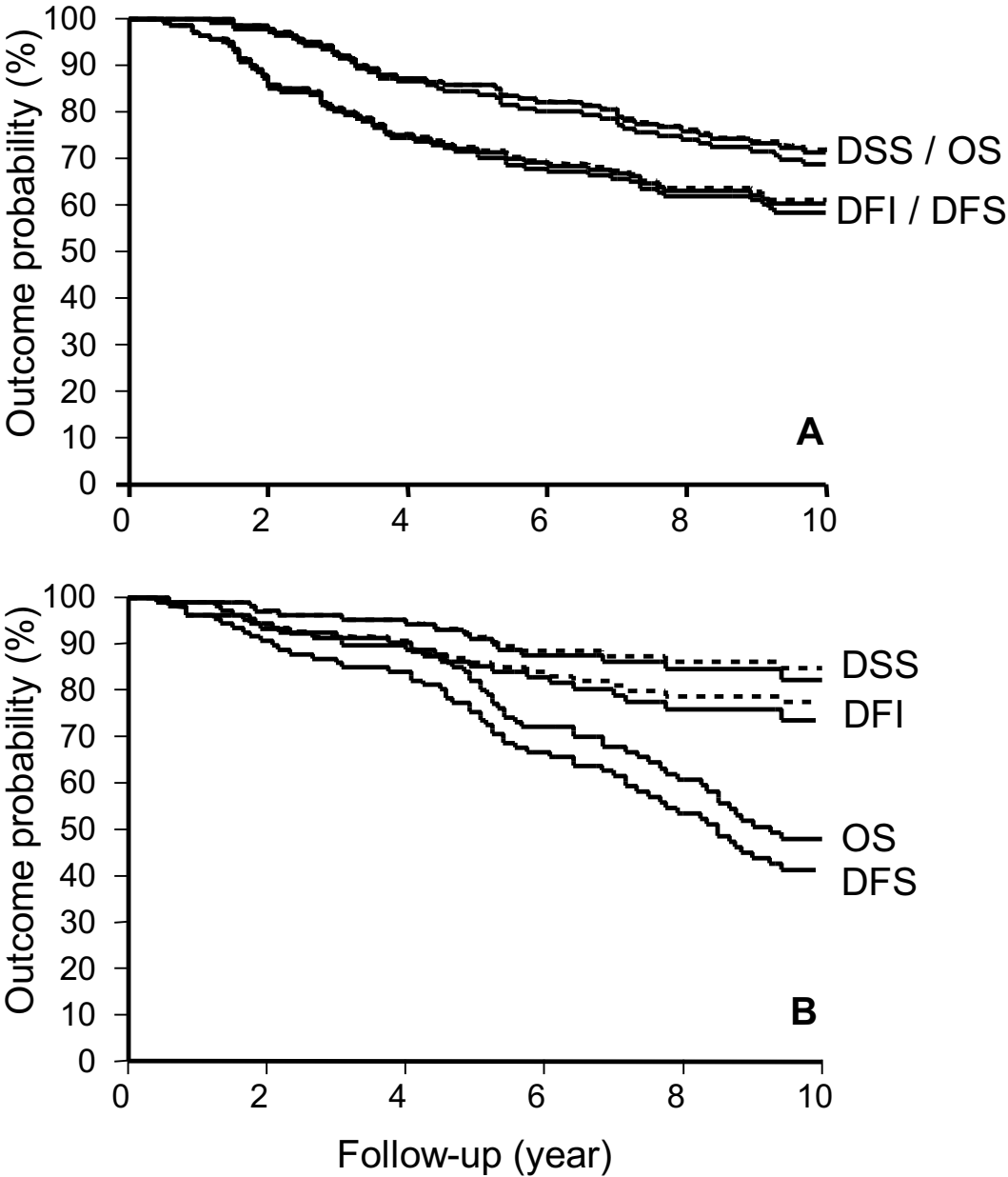
DSS: disease specific survival; OS: overall survival; DFI: disease free interval; DFS: disease free survival.
Contralateral breast cancer was ignored in the definition of relapse.

and 84.9% with Kaplan-Meier and competing risk analyses, respectively. Estimations of 10-year disease free interval were 73.6% and 77.6% respectively for two statistical methods.

Table 3.4. Estimated 10-year event rate according to age at diagnosis determined both by Kaplan-Meier method and competing risk analysis.

Event	10-year event rate (%)					
	≤ 50 yr		51-70 yr		> 70 yr	
	KM	**CR**	**KM**	**CR**	**KM**	**CR**
Overall death	31.1	31.1	23.5	23.5	52.0	52.0
Disease related death	28.6	28.1	16.4	15.7	17.7	15.1
Non-disease related death	3.6	3.0	8.5	7.8	41.7	36.9
Recurrent disease or death	41.5	41.5	32.2	32.2	58.7	58.7
Recurrent disease	39.5	38.8	26.8	25.8	26.3	22.4
Death without recurrent disease	3.2	2.7	7.5	6.5	43.8	36.2

KM: Kaplan-Meier method; CR: competing risk analysis. Recurrent disease was defined as either local recurrence, regional recurrence or distant metastasis whichever came first. Occurring contralateral breast cancer was ignored.

Contralateral breast cancer

We evaluated the effect of the inclusion of contralateral breast cancer as event in the analysis of disease recurrence on estimated disease free interval and disease free survival (Table 3.3). The administration of adjuvant systemic therapy is known to reduce the risk of contralateral breast cancer.[12,13] In the whole study

population the absolute reduction in disease free survival or disease free interval due to inclusion of contralateral breast cancer as event in the definition of relapse was approximately 4%; in patients not treated with adjuvant systemic therapy 6-7%, and in patients treated with adjuvant systemic therapy 1-2%. In the broadest definition of relapse 197 events were counted during 10-years follow-up, including 47 non-disease related deaths and 26 contralateral breast cancers. That is, in the analysis of disease free interval 17% of events were contralateral breast cancers, compared with 13% in the analysis of disease free survival. Consequently, the effect of the inclusion of contralateral breast cancer as event in the definition of relapse was greater when estimating disease free interval than when estimating disease free survival (Table 3.3).

Similarly, the greatest effect of the inclusion of contralateral breast cancer and non-disease related death as events on estimated disease recurrence rate was found in patients with low risk breast cancer. In a subgroup of 168 patients with T1N0 breast cancer, not treated with adjuvant systemic therapy, the 10-year relapse rate including local relapse, regional relapse, or distant metastasis was 23%. The estimated 10-year relapse rate rose to 31% both with the inclusion of either contralateral breast cancer or non-disease related death as event in the definition of relapse, and to 38% with the inclusion of both events in the definition of relapse.

DISCUSSION

In the present study we show in a cohort of patients with early breast cancer that the inclusion of contralateral breast cancer or non-disease related death as event in the definition of recurrent disease or survival strongly affects estimated outcome probability. The magnitude of the effect is dependent on patient-, tumour-, and treatment characteristics.

These findings, and the explicit definition of outcome seem of minor importance for the interpretation of a particular clinical trial as long as results are not compared with other trials. After all, all study arms use the same definition(s) of outcome. However, the effect of the intervention can be different for the various events that are counted, ignored or censored in the definition of outcome. As a consequence, the in- or exclusion of contralateral breast cancer or non-disease related death in the definition of outcome could influence the results of a trial. We can illustrate this with data from the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial.[14,15] 6241 patients are included in the 2 relevant arms of this trial. After a median follow-up of 68 months, 831 patients have died (411 patients treated with anastrozole and 420 patients treated with tamoxifen). More patients who were treated with tamoxifen died from breast cancer than patients who were treated with anastrozole (265 vs. 235), whereas fewer patients who received tamoxifen died from a cause not related to breast cancer (155 vs. 176). Treatment with anastrozole also led to a reduction in disease recurrences (402 vs. 498). A considerable part of this reduction was caused by the difference in occurrence of contralateral breast cancers (35 vs. 59). Consequently, anastrozole led to an improvement in disease free survival (Hazard Rate (HR) 0.87, p=0.01), and an even better improvement in disease free interval (HR 0.79, P=0.0005). Overall survival was similar for anastrozole and tamoxifen treated patients (HR 0.97), whereas disease specific survival was 12% better in the anastrozole group, although this was not significant (HR 0.88, p=0.20). These data from the ATAC trial illustrate that a clear definition of survival endpoints, including the contribution of non-disease related death and the contribution of contralateral breast cancer to the estimated disease recurrence rate are crucial for a correct interpretation of outcome analyses in clinical trials. These data also demonstrate that a significant difference in disease free survival is not automatically followed by a difference in overall survival.

The Kaplan-Meier method for estimating survival has repeatedly been criticised for possible biases in the estimation of event rates.[9,11,16] In the presence of competing events, cumulative incidence functions of the events of interest are probably evaluated more appropriately by taking into account other events within a competing risk framework. In general, event rates derived using the Kaplan-Meier approach are larger than estimates accounting for competing risks,[9,11] and differences between Kaplan-Meier and competing risk approaches can become substantial when the competing risk event is related to or is a result of the underlying disease. But, as presented by Satagopan et al., ignoring the informative censoring mechanism does not substantially influence the estimates of breast cancer-specific mortality.[9] We present similar results in our estimations of disease-specific survival and disease free survival. However, differences became more substantial when relative more patients were censored due to competing events.

In conclusion: Clear definitions of endpoints and competing events are crucial for the interpretation and comparison of outcome studies. In the present study on patients with early breast cancer, the inclusion of contralateral breast cancer and/or non-disease related death substantially influenced estimates of recurrent disease rate and survival, specifically in elder patients and patients with a good prognosis. Bias generated by the Kaplan-Meier approach due to informative censoring of contralateral breast cancer or non-disease related death was limited.

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