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Original paper

Outcome of per protocol best-evidence based routine breast cancer care in a large regional hospital in Belgium: the importance of a prospective database in quality assurance

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Abstract

Aim: Criteria for future accreditation of breast cancer centres in Belgium will be mainly based on the case load per surgeon or per centre. We would like to argue that the prospective collection of relevant data and the analysis of treatment related outcome derived from these data is feasible and should be the ultimate criterion for quality assessment and thus for accreditation since outcome is a more direct measurement of quality.
Methods: Data were prospectively collected on 715 invasive non metastatic breast cancers between 2002 and 2007 treated according to standard, best-evidence protocols in the setting of a large district hospital. Univariate and multivariate survival analysis were performed and compared to national and international databases.
Results: 5 year disease-free survival (DFS) and overall survival (OS) in our series were respectively 77 and 84%. In the multivariate analysis of DFS, only her-2-neu status (her-2-neu positivity being associated with a poor prognosis) and age (older age being a worse prognostic factor) were statistically significant prognostic factors. For OS, her-2-neu, age, and positive nodes were statistically significant prognostic factors. The outcome is comparable to other data sets.
Conclusion: Centres dedicated to the care of women with breast cancer have the moral duty to produce outcome based results of their treatment. This report shows that such a collection of data is feasible and can be imposed as a prerequisite for accreditation. We also argue that outcome based data of treatment are a more solid base for quality assurance than case load.

Key words: Accreditation, breast neoplasms, database, survival, multivariate, prospective, quality control.

Introduction

Recently, the Belgian government issued a bill regulating the organisation of and minimal requirements for specialist breast units (KB, 2007). The criteria were much based on a EUSOMA (European Society of Mastology) position paper (EUSOMA, 2000; Perry, 2001), a text which was adopted in a resolution on breast cancer by the European Parliament. This implied that criteria for accreditation were defined based on minimal standards to ensure high quality of care for women with breast cancer. A lot of attention was given to case load per surgeon and the limit of at least 150 newly diagnosed cases of primary breast cancer per year per centre was subject to much debate. A survey on caseload and surgery for some cancers (one of them breast cancer) was published recently by KCE (Federal Expertise Centre for Health Care), an advisory committee of experts that provides scientific evidence to guide

decision making in health issues by the government. This survey supports an association between caseload and improved outcome (Vrijens *et al.*, 2009). We believe, however, that caseload as a surrogate marker of quality of care is inferior to a direct audit of outcome of treatment. Measurement of outcome is essential for quality control. Therefore prospective registration of relevant clinical, treatment-related, and follow-up data is mandatory and is indeed one of the EUSOMA recommendations for specialised breast units. The EUSOMA consensus group published guidelines "setting out the objectives which loco-regional treatment in breast cancer should meet and to determine the outcome measures to these objectives." In this way each centre with good prospective registration is able to set its outcome against these guidelines as an objective quality control (Rutgers, 2001). We report on the feasibility of such a prospective registration of treatment outcome and discuss the results relative to the outcome of breast cancer care as published in the Flemish cancer registry (Van Eycken and De Wever, 2006).

Patients and Methods

Patients with breast cancer are diagnosed and managed in our unit according to standard treatment protocols based on the best evidence available at the time. These protocols are widely used within the Leuven Hospital Network, a regional network of eighteen hospitals in Flanders aiming at optimising quality and efficiency in health care, training, research, and management. A total of 37 characteristics per patient, including data on demographics, medical history, co-morbidity, staging findings, histology, multi-disciplinary treatment decisions, and post-therapy follow-up are prospectively recorded in an electronic database. The database is managed and updated by one of the authors (JV) at the time of a new follow-up visit. Follow-up attendance in our region is excellent with exceptional losses to follow-up. Women who were not seen at our clinic within the scheduled follow up interval (mostly 12 months) were considered lost to follow-up and data on their health status were retrieved via the family physician in most cases. Logistic regression was used to examine relations between clinical and demographical variables and binary responses.

We focus on two outcomes of interest: overall survival (OS) time and disease-free survival (DFS) time. OS was defined as time (in months) from diagnosis until death from any cause. Patients who were alive at the end of their follow-up were considered censored observations. DFS was defined as time (in months) from start of treatment until tumour recurrence or death. Patients who were alive without tumour recurrence at the end of their follow-up were considered censored observations. Univariate analysis of survival was performed by using the Kaplan and Meier estimates of survival curves and the log rank test. Multivariate analysis of survival was conducted by using Cox's proportional hazard model. All computations were performed by using SAS® v.9.1.3 software. The results of statistical significance tests were assessed by using the 0.05 two-sided significance level.

Results

During a 6-year period between January 2002 and December 2007, a total of 859 newly diagnosed patients with primary breast cancer were treated in our unit. Of these, 76 (8.8%) presented with a carcinoma in situ lesion and 48 (5.6%) were primarily metastatic breast carcinomas. For the purpose of this report, we consider only patients with invasive non-metastatic carcinomas. Among the 735 operated patients, complete data were obtained for 715 patients. Out of the 715 patients, 60 died, while 99 died or experienced tumour recurrence. Median follow-up for patients without recurrence was equal to 33.4 months and for those still alive it was equal to 34.4 months. We serve a population of breast carcinoma patients that is similar to other series (Soerjomataram *et al.*, 2008) : two thirds of women are menopausal with a median age of 57 years (SD = 12.81); 91% of tumours are ductal adenocarcinomas; 60% of tumours were detected as stage T1 disease; 70% of tumours are oestrogen-receptor positive. During the reported observation period, the proportion of breast conservation surgery remained unchanged and was equal to 57% for the entire group. Although there was a tendency towards a more extensive use of breast conservation surgery in the group of patients over the age of 60 years, as compared to the group of patients of age less than 60 years, the difference was not statistically significant (based on a logistic regression model with the year of diagnosis and age, with cut-off at 60 yrs, as covariates).

Two major developments in breast cancer care changed our management protocol during the study period: i) the sentinel node technique, introduced in the period from 2002-2003; and ii) the use of trastuzumab in the adjuvant setting. At present, the sentinel node technique is used in 63 % of women undergoing surgery. The shift in the use of type of axillary surgery is similar in both the younger (< 60 years) and older (> 60 years) patients. Over time, the average tumour size, for which a sentinel node technique was selected, increased from 12 mm to 17 mm. In the last 3 years, tumour size average

Table 1. — Sentinel node detection rate and outcome: evolution over time.

Year	Sentinel node outcome		
	negative (%)	**positive** (%)	**failed** (%)
2002	6 (67)	3 (33)	0 (0)
2003	22 (67)	8 (24)	3 (9)
2004	32 (65)	8 (16)	9 (18)
2005	45 (66)	17 (25)	6 (9)
2006	47 (66)	19 (27)	5 (7)
2007	67 (87)	9 (12)	1 (1)

has stabilized. Table 1 illustrates the learning curve in adopting the sentinel technique in our service: an increasing detection rate and number of procedures with a decreasing percentage of positive nodes. In 32 (50%) cases with a positive sentinel node that underwent axillary node dissection, the sentinel node was the only positive node found.

The FISH technique for determining Her-2-neu receptor status became routine in our practice in 2005, at the time when trastuzumab was approved for the adjuvant treatment of her-2-neu positive breast cancer by the European Medicines Agency. The number of breast cancers that tested FISH-positive for her-2-neu receptor in our series is 16.8%.

The 5-year disease-free survival and overall survival in our series were respectively 77% and 84%. Table 2 presents the univariate analysis for both OS and DFS. Except for histology, tumour grade, and axillary surgery, all prognostic factors reached significance in this analysis. In the multivariate analysis of DFS, only her-2-neu status (her-2-neu positivity being associated with a poor prognosis) and age (older age being a worse prognostic factor) were statistically significant prognostic factors (Table 3). For OS, her-2-neu, age, and positive node status were statistically significant prognostic factors (Table 3).

Discussion

Our report focuses on routine breast cancer care to the best-of-evidence and self-initiated clinical research rather than on data from a multi-centre trial to explore new standards of therapy. An extensive Medline literature search revealed no reports on the results of routine breast cancer care according to current practice in a single centre. However, it is precisely this type of care, to which the majority of women with breast cancer present themselves. There are potential limitations (selection of specific patients) inherent to the experimental setting that can affect the validity generalization of research results. Our data are important as they reflect an "*in vivo*" testing of the evidence and could be regarded as an example, to which the outcome of routine breast cancer care within a comparable demographic setting could be compared.

We have shown that it is feasible to run a proper outcome-based database of all patients managed within a specialized breast unit, as it is envisaged by EUSOMA guidelines (Blamey and Cataliotti, 2006). Belgian legislation concerning accreditation of specialized breast units, however, mainly focuses on case load per surgeon as a primary qualification criterion (EUSOMA, 2007). We like to argue that treatment outcome is a better reflection of quality of breast cancer care than is case load per surgeon or per hospital. First and foremost, case load is a surrogate marker, while outcome, measured in terms

Table 2. — Results of the logrank test (*P*-vaues) for the univariate analysis of clinical characteristics for disease-free survival and overall survival.

Variable	Disease-free survival	Overall survival
Increasing Age	0.0001	0.0001
Post Menopausal state	0.0068	0.0037
Histology	0.7797	0.9523
Tumour grade	0.2613	0.7730
Increasing Tumour size	0.0001	0.0001
Positive nodes	0.0001	0.0015
Oestrogen receptor negative	0.0011	0.0109
Progesterone receptor negative	0.0001	0.0001
Her-2-neu receptor positive	0.0001	0.0001
LVI* present	0.0001	0.0105
Breast surgery (mastectomy worse)	0.0001	0.0001
Axillary surgery(ALND**)	0.0552	0.1115

* LVI: lymphvascular space invasion
ALND: Axillary lymph node dissection versus sentinel node procedure.

Table 3. — Multivariate analysis of disease-free DFS and overall survival OS.

Variables DFS	Estimate	Standard error	*P* value	Hazard rate	95% Hazard rate confidence limit
Her-2-neu	-1.3376	0.31664	0.0001	0.262	0.141-0.488
Age	0.02955	0.01135	0.0092	1.030	1.007-1.053
Variables OS					
Her-2-neu	-1.1421	0.4158	0.0060	0.319	0.141-0.721
Age	0.0689	0.0157	0.0001	1.071	1.039-1.105
Positive nodes	0.0976	0.0344	0.0046	1.103	1.031-1.180

of either overall or disease-free survival, is a direct parameter related to treatment effectiveness. Although high surgeon- or hospital volume contributes significantly to patient outcomes, no clear critical volume thresholds associated with substandard breast cancer care have been described (Allgood and Bachmann, 2006). Caseload improves clinical skills indeed but it could be argued that this is less relevant to experienced breast surgeons. Treatment outcome is also influenced by good clinical (surgical) skills, irrespective of caseload (Zork *et al.*, 2008). We are obviously in search for an accreditation system based on criteria that also select for good clinical skills. Treatment outcome in breast cancer care is the overall result of the combined skills not only of breast surgeons, but also those of radiotherapists and medical oncologists. For these reasons, an accreditation system based on the case load per surgeon as a single determinant does not necessarily guarantee optimal assessment of a centres performance.

Five-year DFS and OS for the total population in our series were equal to 77% and 84%, respectively, and compare well with national and international registries. The global 5-year survival and the 5-year relative survival in the Flemish Cancer Registry are 82% and 75%, respectively (Van Eycken and De Wever, 2006). In the SEER data, 5-year relative survival is equal to 88% (Horner *et al.*, 2009). These numbers cannot be compared directly, because relative survival represents breast cancer specific survival by dividing overall survival by the background survival in the population, a number unknown to us. In addition, we did not take stage IV into account. A comparison of the survival stage by stage between our data set and that from the Flemish Cancer Registry is however possible and is shown in Figure 1.

Comparison with large data sets, such as the Flemish Cancer Registry and the SEER data, enables to detect differences in outcome and/or to understand differences in populations. Should outcome be inferior to what is expected in a specific population, one should institute a critical case review of all treatment failures in order to correct possible errors. Such an outcome evaluation should be done periodically in every specialized breast unit by the healthcare authorities. Whether it is appropriate to make data on provider performance available to the public is still a matter of debate (Chen *et al.*, 2008; Mannion and Goddard, 2001; Marshall *et al.*, 2000). We also recommend internal audits, in particular, at the time of management changes, for instance the introduction of a new surgical technique. An example is the sentinel procedure. We have seen a clear improvement of detection rate without increase of positive cases in our series. This reflects good patient selection (Table 2). Nevertheless, the opposite could have been true and this should be anticipated in an early stage to avoid potential deterioration of outcome over time.

Most patient and tumour characteristics, as described in our series, reflect those presented in other breast cancer populations (Soerjomataram *et al.*, 2008). There are, however, some remarkable findings: the univariate analysis reveals no significant prognostic value for tumour grading. This is in contrast to the well validated Nottingham prognostic index (Galea *et al.*, 1992). This might be due to chance, the results of the analysis may be confounded by the tumor-grade-based selection of treatment regimen, which might remove the prognostic value of the tumor grade or to a lack of power. The reasonable large number of tumours designated to grade III (grade I: 12%; grade II: 49%, grade III: 35%; grade unknown: 4%) suggests that the lack of an association with outcome is not caused by overrepresentation of grade II tumours.

The multivariate analysis indicates that older age, positive node status, and FISH-positive Her-2-neu receptor status are the most important prognostic factors with regard to outcome.

We have no formal proof that evaluation of outcome should replace case load as the primary criterion for accrediting breast cancer centres as this study was not designed to do so. However the mere fact that we demonstrated that an outcome based evaluation is feasible in a centre dedicated to breast cancer care moderates the relevance of this

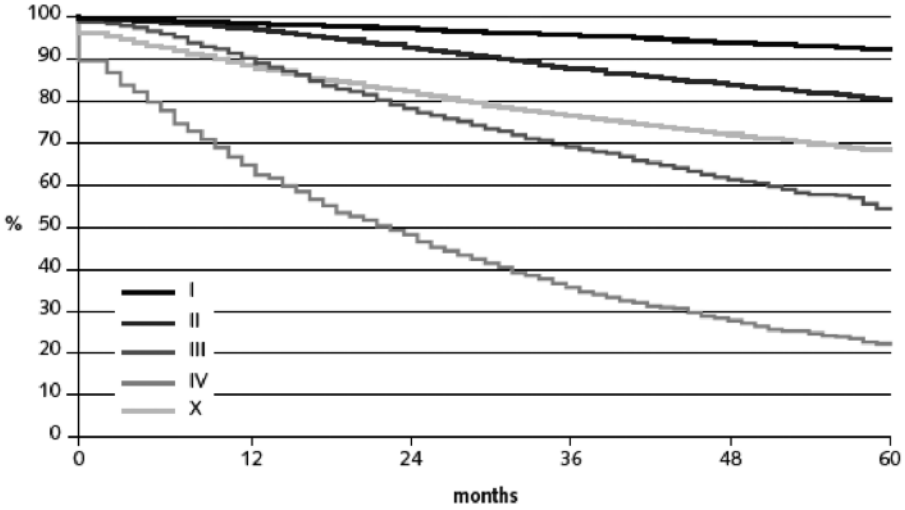

Fig. 1a. — Overall survival per stage in Flanders 1997-2001: data from the Flemish Cancer Registry

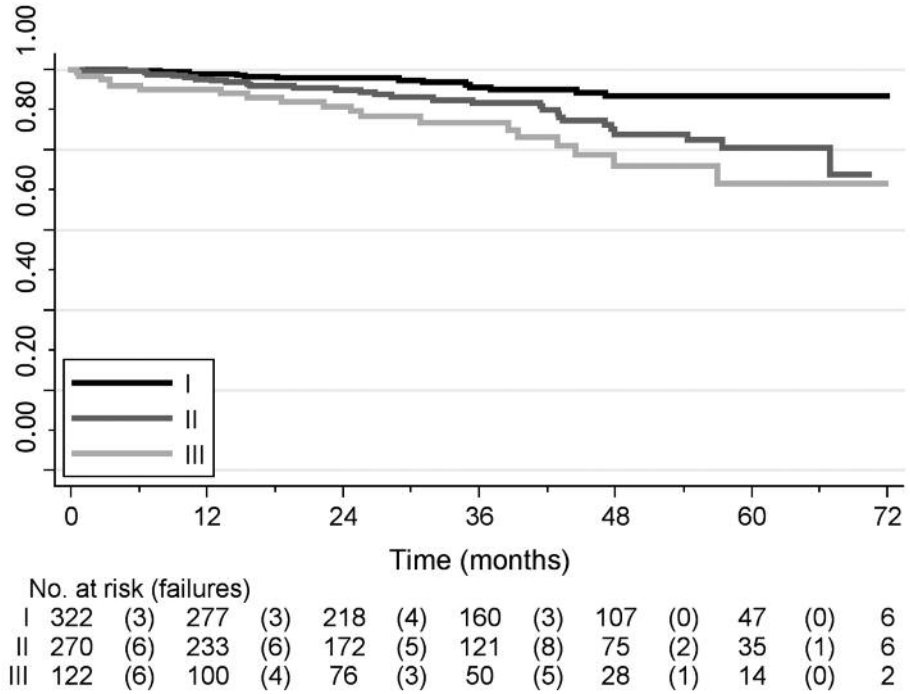

Fig. 1b. — Overall survival per stage (I-III) in our centre

discussion. Moreover Belgium has an electronic network in place between the population registry, the national health insurance system and the national cancer registry that is capable of doing this monitoring nationwide. We acknowledge that monitoring quality of care by outcome is far more complex and expensive than monitoring case load.

In conclusion, we showed that it is feasible to run an up-to-date clinical database in a district hospital. Such a database enabled us to present data on outcome. These data allowed us to infer that the quality of care offered to women with breast cancer in our hospital is conform to national and international standards. Case load remains an essential prerequisite for accreditation. We argued the pros and cons of accreditation of specialist breast units based on the performance of the multidisciplinary team measured by outcome versus case load per hospital or surgeon.

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