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Original article

Translating the concept of intrinsic subtypes into an oncoplastic cohort of more than 1000 patients – predictors of recurrence and survival

M. Rezai [a, 1], S. Kellersmann [a, b, 1, 2], S. Knispel [a, b, 1, 2], H. Lax [c, 3], R. Kimmig [b, 2], P. Kern [a, b, *, 2]

[a] Breast Center Düsseldorf Luisenkrankenhaus, Director: Dr.Mahdi Rezai, Hans-Günther-Sohl-Str.6-10, 40235 Düsseldorf, Germany
[b] University Hospital of Essen, Department of Gynecology and Obstetrics, West German Cancer Center, Hufelandstr.55, D-45147 Essen, Germany
[c] Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), Zweigertstr. 37, D-45130 Essen, Germany

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ABSTRACT

Introduction: A paradigm shift in breast cancer was introduced by Sørlie's concept of intrinsic subtypes [1]. We validated this concept – which was originally based on 84 individuals – in a large cohort study of 1035 patients with oncoplastic surgery and analyzed if early and late recurrences are linked to a specific intrinsic tumor subtype or resection margins.

Materials and methods: 1035 patients with oncoplastic surgery (2004–2009) were analyzed with regard to treatment characteristics and patterns of early (<5 years) and late recurrence (>5 years) and survival related to the intrinsic subtypes. Data was retrieved from patient's charts, customized patients questionnaires and cancer registries.

Results: 944 patients with primary, unilateral breast cancer, median age 58 years, were eligible for analysis. At a median FU of 5.2 years, LRR was 4.0%, 5-year-OS 94.5% and DFS 90.9%. Intrinsic subtypes, but not T-size, nodal-status, resections margins nor histopathology, governed local control and survival. There was no signal for prevelance of unclear margins in any of intrinsic subgroups and no preference of any oncoplastic technique attributed to them. TNBC and Her2 non-luminal breast cancer had highest recurrence and lowest survival rates. Although sentinel involvement (SLN+) was prevailing in the Luminal-B-Her 2 negative subtype at 34.3%, this did not translate into a higher axillary dissection rate.

Conclusion: This study confirmed the intrinsic subtype concept on a large clinical basis and describes the patterns of early and late recurrence in oncoplastic surgery, concluding that bigger risk may not be overcome by bigger surgery.

Introduction

Various oncoplastic techniques have evolved in the last decades and former concepts attributed high oncologic safety to a high extent of surgery in breast cancer (BC). Determinants of local control were mainly considered to be T-size, resection margins and nodal status until the intrinsic subtype concept by Sorlie T. et al. in 2001 has been introduced [1]. In this study, we investigated different surgical techniques in relation to intrinsic subtypes, as each of these subtypes yields different recurrence rates. This may lead to surgeons' assumption that also clinicopathological features of these subtypes may vary in the sense of higher occurence of multicentricity, presence of unclear margins, re-excision rate and nodal involvement. Surgeons may be tempted to try to overcome “bigger risk” by applying “bigger surgery” [2], with a predilection for bigger margins or mastectomy in high-risk intrinsic subtypes. The question remained whether recurrences occur due to intrinsic biology and/or unclear margins and whether tumor biology may be overturned by applying extensive surgery as postulated by the Halstedian dogma in the last century. Sorlie's milestone paper was originally based on a

* Corresponding author. Breast Center Düsseldorf Luisenkrankenhaus, Director: Dr. Mahdi Rezai, Hans-Günther-Sohl-Str.6-10, 40235 Düsseldorf, Germany. Tel.: +49 (0) 211 44774400; fax: +49 (0) 211 44774499.
[1] Tel.: +49 (0) 211 44774400; fax: +49 (0) 211 44774499.
[2] Tel.: +49 (0) 723 85280.
[3] Tel.: +49 (201) 723 92239250.

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cohort of 84 patients [1]. We translated this concept into a cohort of more than 1000 oncoplastic patients in order to analyze whether this concept may be confirmed in the framework of oncoplastic techniques and if oncoplastic breast conserving techniques are valid options for dealing with all intrinsic subtypes at a high degree of local and systemic control. We assessed recurrence rates (early: <5 years, late: > 5 years), DFS and OS and related it to intrinsic subtypes, grading, T-size, nodal-status, resection margins and histopathological subtypes.

Patients and methods

Patient cohort

A total of 1035 patients with BC and oncoplastic surgery from 2004 to 2009 were identified for this study. Inclusion criteria were unilateral, non-metastasized primary BC and 944 patients finally fulfilled these criteria. Patient and treatment characteristics as well as survival data were retrieved from patient records, customized questionnaires and cancer registries. The study was approved by the institutional review board and complied with the declarations of Helsinki and the principles of good clinical practice.

Tumor classification

Tumors were classified according to TNM-system [3] and analyzed in a central pathology. Grading was classified according to Elston and Ellis [4]. ER and PR status of BC specimen included in our study were considered as positive if ≥10% of BC cells expressed ER and/or PR, in accordance with the AGO and ASCO/CAP guidelines at the time of patient enrollment for treatment [5,6]. Her2-status was considered as positive if DAKO-Score was 3+ or FISH-analysis was positive in DAKO-Score 2+ [6].

As Ki-67 was not available for all patients of the cohort, we used 2011 St. Gallen International Expert Consensus Guidelines to classify histological approximated intrinsic subtypes: luminal A (ER^+ and/or PR^+, $ERBB2^-$, grade 1/2), luminal B HER2 negative (ER^+ and/or PR^+, $ERBB2^-$, grade 3), luminal B HER2 positive (ER^+ and/or PR^+, $ERBB2^+$), HER2 non luminal (ER^- and PR^-, $ERBB2^+$, all grades) or TNBC (ER^- and PR^-, $ERBB2^-$) [7].

Statistics

Data was entered into a Microsoft Office Excel 2007 database, and analyses were performed using SAS Version 9.2. Local control parameters were calculated in a univariate and multiple analysis. All patient characteristics were presented in frequency tables and compared by univariate testing (Wilcoxon rank sum and chi-square tests). Patient numbers refer to a total of 944; calculating percentages includes missings. Survival was estimated and plotted by using Kaplan–Meier analysis. Log-rank test and Wilcoxon-rank sum tests were used. Multiple Cox proportional hazards regression models were used for estimating age-adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). All p-values were given descriptively without further adjustment for multiple testing.

Results

Patients baseline characteristics

A total of 944 patients met inclusion criteria. 70.7% was the questionnaire response rate. Median follow-up was 5.2 years.

Table 1
Patient characteristics.

Characteristics	Number of patients	Percentage (%) of n = 944
Age		
<30 years	7	0.7
30–39 years	41	4.3
40–49 years	190	20.1
50–59 years	261	27.7
60–69 years	305	32.3
70–79 years	128	13.6
≥80 years	12	1.3
T-size		
Tis	110	11.7
T1mic	4	0.4
T1a	28	3.0
T1b	113	12.0
T1c	417	44.2
T2	209	22.1
T3	3	0.3
T4	3	0.3
Unknown	57	6.0
Nodal status		
N0	665	70.4
N1	24	2.5
N1a	109	11.6
N2	0	0
N2a	34	3.6
N3	0	0
N3a	10	1.1
Unknown	102	10.8
Grading		
G1	97	10.3
G2	620	65.7
G3	201	21.3
Unknown	26	2.7
Resection margin		
R0	910	96.4
R1	14	1.5
Unknown	20	2.1
Histology		
Invasive ductal	572	60.6
Invasive lobular	110	11.6
Invasive with other Histology	129	13.7
Non-invasive	110	11.7
Unknown	23	2.4

Average age was 57.6 years (median 58, range 25–88 years) (Table 1).

Tumor localisation

The most common tumor localization was the upper outer quadrant with 36.5% (Fig. 1.), 11.7% were multifocal or multicentric.

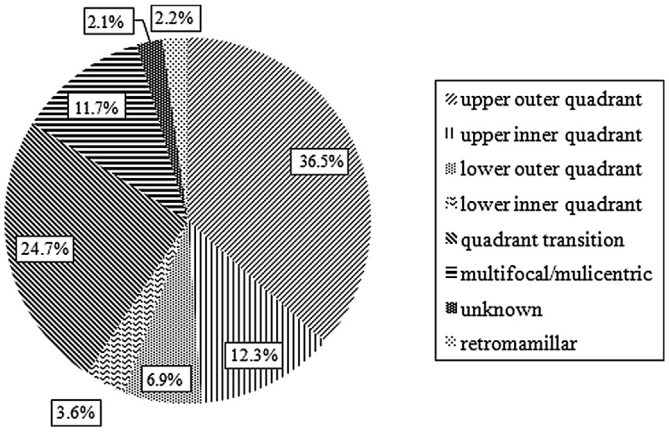

Fig. 1. Distribution of tumor locations in the breast.