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Clinicopathological characteristics and outcome of high grade breast cancer: our 9 years' experience

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Summary

Introduction: The aim was to determine the characteristics of G3 breast cancers as well as to evaluate the treatment patients received and their outcome in terms of overall- and disease-free survival. *Materials and Methods:* 2,407 women affected by invasive breast cancer were retrospectively analyzed. Patients were divided into three groups according to the grading, to compare G3 cancers with G1 and G2 ones. Tumor, population characteristics, management, and outcomes were considered in the analysis. *Results:* The authors found that G3 breast cancers were associated with tumor characteristics indicative of more aggressive behavior and with reduced overall and disease-free survival. Although they were more frequently treated with demolitive surgery and chemotherapy, prognosis of G3 tumors at Stages I and II did not change in case of radical or conservative surgical treatment, while Stage III G3 tumors had a significant prognostic advantage by conservative surgery. *Conclusions:* G3 breast cancers should be considered with particular attention for their aggressiveness when planning the therapeutic procedure. However, breast demolitive surgery should be carefully scheduled and reserved to women who can not benefit from complementary therapies to conservative surgery.

Key words: Breast neoplasms; Neoplasm grading; High grade breast cancer; Breast conservative surgery.

Introduction

A great number of histopathologic features and biomolecular markers have been studied during the last decades in order to detect risk factors for local and distant recurrences, and consequently to predict breast cancer behavior and response to the therapies [1–4]. The histologic grading represents one of this factors, being the expression of the proliferative ability of neoplastic cells.

Histologic grading is calculated through the evaluation of three characteristics of breast cancer cells, including mitotic count, nuclear pleomorphism, and tube formation (considering the amount of tumor tissue with normal duct structure). The sum of these values may vary between 3 and 9 points and determines a score which allow cancers to be classified within three grades: low grade (G1), moderate grade (G2) and high grade (G3) [5, 6].

Due to its somewhat subjective assessment, histologic grading has often been criticized for poor reproducibility and lacking agreement among different observers [7]. Nonetheless, despite the apparent difficulties in using grade as prognostic tool, when performed by experienced pathologists in single institutions, it significantly correlates with patients clinical outcome [5, 6, 8–15].

The present study aims to determine the characteristics of G3 breast cancers, including their clinical presentation and their pathological aspects, as well as to evaluate the treatment patients received and their outcome in terms of overall- and disease-free survival.

Materials and Methods

The authors collected retrospective data regarding 2,407 women operated on their breast for invasive breast cancer in the Clinic of Surgery between 2002 and 2010 in order to have at least four years of follow up. Invasive breast cancers included invasive ductal carcinoma, invasive lobular carcinoma, invasive ductal and lobular carcinoma, and all invasive breast cancers other than ductal and lobular. Intraductal neoplasia and benign breast lesions were excluded from this study. This study follows the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority.

The authors took into consideration patients characteristics as follows: age and BMI at the time of diagnosis, familial history of breast cancer, menopause. and the use of hormonal oral contraceptives. Among tumor characteristics they considered: histological type, TNM classification and stage, eventual extra-axillary lymph node involvement (internal mammary chain and subclavian), nuclear grading, Mib 1/Ki 67 proliferation index, and estrogen and progesterone receptors expression, Her2/neu status, and molecular subtypes. They also took into consideration, as previously described, other microscopical histological characteristics which are included in a more recent classification purposed by Veronesi *et al.* including multifocality/multicentricity, extensive intraductal component (EIC), perivascular invasion, peritumoral

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Table 1. — *Description of the population by tumor grade. The significance tests used in this Table are One Way ANOVA, Kruskal-Wallis test or chi-square test.*

	G 1	G 2	G 3	*p*
Age (years)	60.84 (±11.18)	61.3 (±12.77)	58.68 (±13.96)	<0.05
BMI (kg/m²)	25.85 (±4.88)	26.06 (±4.83)	25.81 (±4.96)	0.564
Median follow-up (months)	81 (62-112)	87 (68-115)	83 (59-110)	<0.05
Median follow-up before metastases (months)	48 (18-60)	22 (8-56)	21 (0-44)	0.433
Tobacco smoke	5.7% (16/281)	5.8% (68/1177)	4.3% (23/541)	0.411
Family history of cancer	31.2% (24/77)	36.2% (113/312)	36.1% (52/144)	0.696
Use of estro-progestinics	20.6% (13/63)	28.6% (76/266)	31.4% (38/121)	0.299
Post-menopausal status	84.7% (250/295)	83.4% (1083/1299)	74.7% (445/596)	<0.05
First breast surgery				
Mastectomy	22.7% (73/321)	36.9% (529/1433)	48.2% (315/653)	<0.05
BCS	77.3% (248/321)	63.1% (904/1433)	51.8% (338/653)	<0.05
Second breast surgery (only BCS)				
Not required	78.6% (195/248)	72.8% (658/904)	64.2% (217/338)	<0.05
Second BCS	13.7% (34/248)	12.4% (112/904)	13.9% (47/338)	0.722
Mastectomy	7.7% (19/248)	14.8% (134/904)	21.9% (74/338)	<0.05
First axilla surgery				
CALND	34% (109/321)	49.5% (709/1433)	66.3% (433/653)	<0.05
SLNB	56.1% (180/321)	42.8% (613/1433)	28.3% (185/653)	<0.05
No axilla surgery	10% (32/321)	7.7% (111/1433)	5.4% (35/653)	<0.05
Second axilla surgery (excluded previous CALND)				
None	87.3% (185/212)	77.2% (559/724)	77.3% (170/220)	<0.05
CALND	12.7% (27/212)	22.8% (165/724)	22.7% (50/220)	<0.05
Non surgical treatments				
Neoadjuvant chemotherapy	3.7% (12/321)	7.2% (103/1433)	12.6% (82/653)	<0.05
Adjuvant radiotherapy	67.4% (207/307)	56.7% (773/1363)	55.1% (347/630)	<0.05
Adjuvant chemotherapy	18.6% (57/307)	38.5% (523/1359)	62.2% (392/630)	<0.05
Adjuvant hormonal therapy	89.5% (274/306)	85.8% (1165/1358)	59.1% (372/629)	<0.05

inflammation, lymph node extra-capsular invasion, and presence of bunched lymph nodes [2–4, 16–19].

Regarding the therapeutic management of these patients, the authors took into account the surgical operation on the breast (conservative *vs.* radical surgery) and the axilla (sentinel lymph node biopsy *vs.* complete axillary lymph node dissection), the eventual administration of radiation therapy, neoadjuvant therapies, adjuvant chemotherapy or hormonal therapy. Then, they divided the patients into three groups according to the grading, and compared G3 cancers with G1 and G2 ones.

The statistical analysis was performed using the program R (version 3.0.1 - http://www.R-project.org/). The normal distribution of variables was assessed by the Kolmogorov-Smirnov test. Where appropriate, the following statistical tests were also utilized: *t*-test, Wilcoxon test, one way ANOVA, Kruskall-Wallis test for continuous variables, chi-square, and Fisher's exact test for categorical variables. To analyze the survival curves, the Kaplan-Meier and the differences between the different groups were evaluated by the log-rank test. In addition, an analysis was performed by mono-and multi-variate regression models using the Cox proportional hazards (Cox proportional hazards regression model).

Results

In this study the authors analyzed 2,407 invasive breast cancers operated in the Clinic of Surgery between 2002 and 2010. Among the considered cancers, 321 (13.3%) were classified as G1, 1,433 (59.5%) as G2, and 653 (27.1%) as G3. Mean patients age at surgery was 60.53 ± 12.96 years and mean BMI 25.96 ± 4.87 kg/m^2. In 73.9% of cases, women were found to be in menopause (Table 1). Median observation period turned resulted to be 85 (64-113) months.

In most cases (61.9%), the first surgical approach was conservative, while mastectomy was performed only in 1,144 (47.5%) women (Table 1). Taking into account axillary surgery, 978 (40.6%) women underwent sentinel lymph node biopsy (SLNB), 914 (38.0%) of which could not avoid the subsequent complete axillary lymph node dissection (CALND) due to negative SLN. Hormonal therapy was performed in 75.2% of cases.

Regarding the histological characteristics of considered tumors, most cases were Stage I infiltrating ductal carcinomas, with positivity for hormone receptors (Tables 2 and 3). If the differences among the three grading were then analyzed, G1 and G2 tumors were significantly more frequently treated with conservative interventions than G3 ones (Table 1). In addition, G3 tumors had a significantly higher prevalence of chemotherapy administration, both as neoadjuvant or adjuvant treatment, while they had a significant lower prevalence of cases submitted to hormonal therapy compared to G1 and G2 tumors (Table 1). In fact, G3 tumors showed a significantly lower prevalence of hormonal receptors' expression (Table 2). Furthermore, G3 tu-

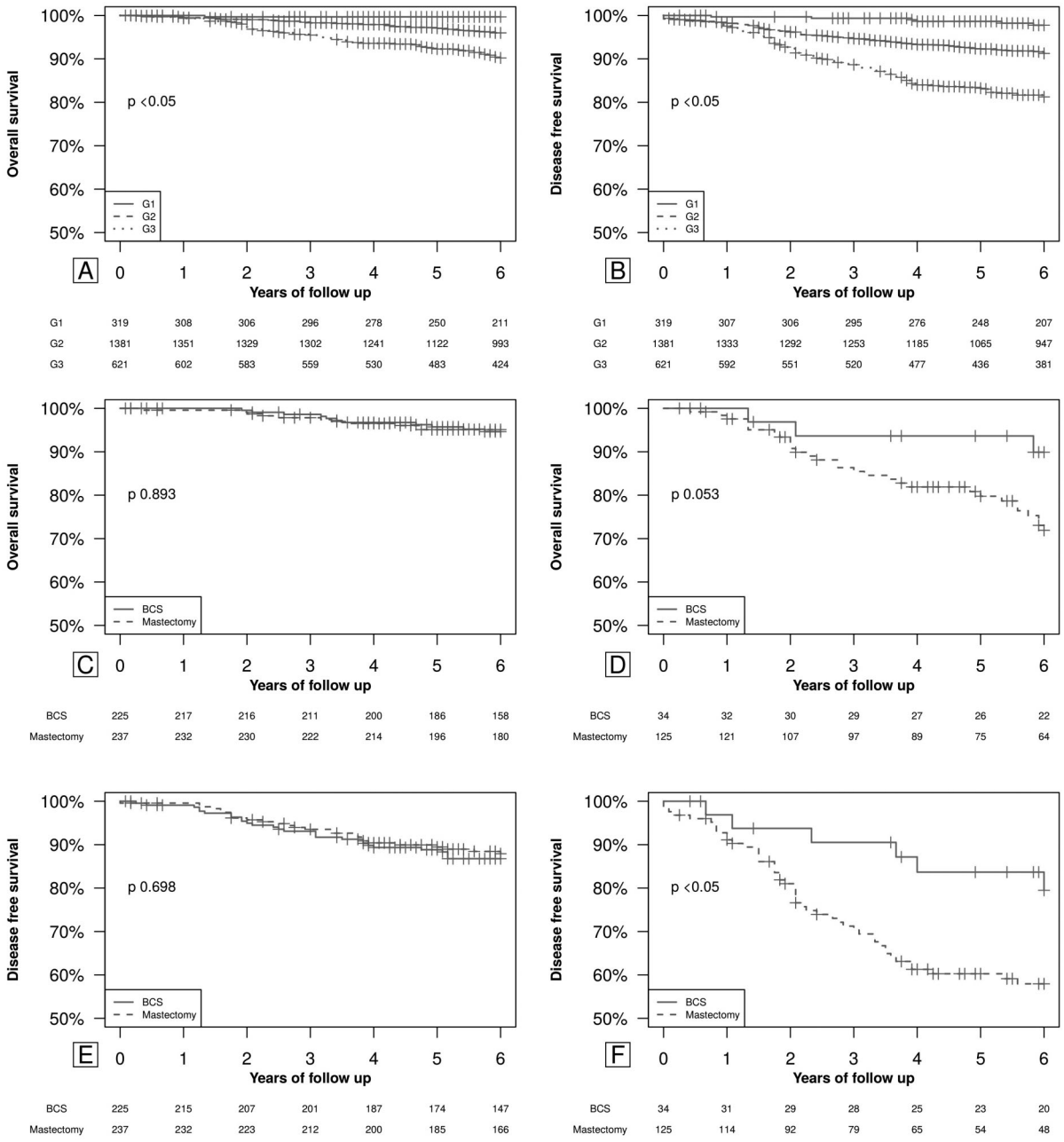

Figure 1. — Kaplan Meier plots. Panel A: Grading and survival. Panel B: Grading and disease-free survival. Panel C: Grading 3 and overall survival in TNM Stages I and II. Panel D: Grading 3 and overall survival in TNM Stage III. Panel E: Grading and disease-free survival in TNM Stages I and II. Panel F: Grading and disease-free survival in TNM Stage III.

mors resulted to have a higher prevalence of Her2/neu expression, as well as of triple negative subtype (Table 2).

Analyzing other histological characteristics, G3 were diagnosed at a significantly more advanced stage than the G1 or G2 (Table 3). In particular, G3 tumors showed a significantly higher prevalence of multifocality/multicentricity, comedo-like necrosis, perivascular invasion and peritumoral inflammation in comparison with G1 or G2 (Table 2). Moreover, G3 tumors presented also a higher prevalence of lymph node extra-capsular invasion (Table 2).

For what regards the prognosis, the multivariate analysis demonstrated that in our population G3 tumors correlated with significantly shorter overall and disease-free survival (Tables 4 and 5) (Figures 1A and 1B). Anyway, selecting only G3 tumors at stage I and II, radical surgery did not correlate with a better prognosis (Figures 1C and 1E), and

Table 2. — *Tumor characteristics and outcome divided by tumor grade. The significance test used in this Table is the chi-square test.*

	G 1	G 2	G 3	*p*
Tumor histology				
Invasive ductal carcinoma	88.2% (283/321)	68.6% (983/1433)	83.5% (545/653)	<0.05
Invasive lobular carcinoma	3.1% (10/321)	18.6% (266/1433)	5.5% (36/653)	<0.05
Invasive ductal and lobular carcinoma	2.5% (8/321)	10.3% (148/1433)	6.9% (45/653)	<0.05
Other invasive carcinoma	6.2% (20/321)	2.5% (36/1433)	4.1% (27/653)	<0.05
Primary tumor characteristics				
Positivity to estrogen receptors	97.5% (306/314)	91.9% (1285/1398)	60.6% (391/645)	<0.05
Positivity to progesterone receptors	86.3% (271/314)	80% (1119/1399)	48.1% (310/645)	<0.05
Positivity to Her2/neu	1.6% (4/253)	8.4% (93/1113)	25.1% (142/566)	<0.05
Mib-1 >20	6.4% (13/204)	28.6% (270/945)	69.6% (327/470)	<0.05
Comedo-like necrosis	3.1% (10/321)	5.2% (75/1433)	15.5% (101/653)	<0.05
Multifocality/multicentricity	13.7% (44/321)	20.7% (297/1433)	25% (163/653)	<0.05
EIC	30.8% (99/321)	26.2% (375/1433)	36% (235/653)	<0.05
Perivascular invasion	4.4% (14/321)	11% (158/1433)	23.6% (154/653)	<0.05
Inflammatory carcinoma	0.3% (1/321)	4% (57/1433)	9% (59/653)	<0.05
Tumor molecular type				
Basal-like	0.9% (3/321)	4% (57/1433)	21.3% (139/653)	<0.05
Her enriched	0.3% (1/321)	1.4% (20/1433)	12.4% (81/653)	<0.05
Luminal A	50.5% (162/321)	32.5% (466/1433)	7.8% (51/653)	<0.05
Luminal B	10.3% (33/321)	24.6% (353/1433)	30.2% (197/653)	<0.05
Luminal Her	0.9% (3/321)	4.9% (70/1433)	9.2% (60/653)	<0.05
Non-descript	37.1% (119/321)	32.6% (467/1433)	19.1% (125/653)	<0.05
Loco-regional extra axillary lymph nodes	2.8% (9/321)	2% (28/1433)	1.5% (10/653)	0.403
Features axillary lymph nodes				
ITC	1.6% (5/321)	2.4% (35/1433)	1.7% (11/653)	0.406
Micrometastasis	4% (13/321)	5.3% (76/1433)	3.7% (24/653)	0.223
Extra-capsular invasion	2.2% (7/321)	7.3% (105/1433)	15.5% (101/653)	<0.05
Bunched lymph nodes	0.3% (1/321)	3.1% (44/1433)	8.1% (53/653)	<0.05
Recurrences in the observation period				
Loco-regional recurrence	1.6% (5/321)	5.4% (77/1433)	9.6% (63/653)	<0.05
Distant metastases	1.6% (5/321)	7.4% (106/1427)	13.2% (86/651)	<0.05

Table 3. — *TNM staging divided by tumor grade. The significance test used in this Table is the chi-square test.*

	G 1	G 2	G 3	*p*
Local tumor extension (T)				
T1	71.4% (1719/2407)	72.2% (1035/1433)	60% (392/653)	<0.05
T2	22.8% (548/2407)	22.4% (321/1433)	30.8% (201/653)	<0.05
T3	1.9% (45/2407)	2% (28/1433)	2.3% (15/653)	0.180
T4	3.9% (95/2407)	3.4% (49/1433)	6.9% (45/653)	<0.05
Loco-regional lymph nodes (N)				
N0	66.2% (1593/2407)	66.2% (949/1433)	57.4% (375/653)	<0.05
N1	21.7% (522/2407)	23.3% (334/1433)	21.9% (143/653)	<0.05
N2	6% (144/2407)	5.9% (85/1433)	8.4% (55/653)	<0.05
N3	6.1% (148/2407)	4.5% (65/1433)	12.3% (80/653)	<0.05
TNM stage				
Stage I	50.4% (1193/2365)	50.679% (709/1399)	36.842% (238/646)	<0.05
Stage II	32.6% (772/2365)	34.596% (484/1399)	34.675% (224/646)	<0.05
Stage III	15.1% (356/2365)	13.438% (188/1399)	24.613% (159/646)	<0.05
Stage IV	0.312% (1/320)	1.287% (18/1399)	3.87% (25/646)	<0.05

Table 4. — *Overall survival and disease free survival univariate (*) and multivariate (**) Cox analysis.*

	Overall survival				Disease free survival			
	HR (95% CI)(*)	$p^{(*)}$	HR (95% CI)(**)	$p^{(**)}$	HR (95% CI)(*)	$p^{(**)}$	HR (95% CI)(*)	$p^{(**)}$
Tumor grading G3	3.18 (2.35-4.30)	<0.05	2.33 (1.39-3.9)	<0.05	2.52 (2.02-3.16)	<0.05	1.37 (0.95-1.96)	0.090
Age	1.01 (1.00-1.03)	<0.05	1.03 (1.01-1.05)	<0.05	0.99 (0.98-1)	0.200		
Post-menopausal status	1.29 (0.80-2.07)	0.302			0.74 (0.54-1.02)	0.066	1.13 (0.76-1.68)	0.541
BCS	0.31 (0.21-0.45)	<0.05	0.72 (0.4-1.31)	0.279	0.35 (0.26-0.46)	<0.05	0.55 (0.37-0.81)	<0.05
Neoadjuvant chemotherapy	3.06 (2.03-4.61)	<0.05	1.91 (1.11-3.27)	<0.05	2.91 (2.1-4.05)	<0.05	2.11 (1.35-3.29)	<0.05
Adjuvant radiotherapy	0.60 (0.42-0.85)	<0.05	0.52 (0.31-0.87)	<0.05	1.04 (0.79-1.36)	0.801		
Adjuvant chemotherapy	6.20 (3.95-9.74)	<0.05	3 (1.58-5.68)	<0.05	4.75 (3.47-6.5)	<0.05	2.5 (1.6-3.92)	<0.05
Adjuvant hormonal therapy	0.28 (0.19-0.39)	<0.05	0.71 (0.39-1.29)	0.259	0.38 (0.29-0.51)	<0.05	0.61 (0.36-1.02)	0.061
Tumor histology								
Invasive ductal carcinoma	Reference	1.000			Reference	1.000		
Invasive lobular carcinoma	1.36 (0.85-2.16)	0.195			1.34 (0.94-1.92)	0.106		
Invasive ductal and lobular carcinoma	1.50 (0.88-2.55)	0.132			1.4 (0.92-2.14)	0.114		
Other invasive carcinoma	1.19 (0.48-2.93)	0.704			0.29 (0.07-1.16)	0.080		
Basal-like subtype	3.98 (2.67-5.93)	<0.05	1.25 (0.63-2.51)	0.523	3.03 (2.17-4.25)	<0.05	0.97 (0.5-1.88)	0.934
Positivity to Her2/neu	1.31 (0.8-2.14)	0.280			2.14 (1.53-2.99)	<0.05	1.02 (0.61-1.72)	0.941
Mib-1 >20	2.95 (1.92-4.52)	<0.05	1.20 (0.72-2.00)	0.491	3.87 (2.78-5.4)	<0.05	1.63 (1.09-2.46)	<0.05
Comedo-like necrosis	0.93 (0.49-1.76)	0.818			1.66 (1.12-2.47)	<0.05	1.54 (0.92-2.58)	0.098
Multifocality/multicentricity	1.15 (0.77-1.7)	0.500			1.14 (0.84-1.55)	0.410		
EIC	0.59 (0.39-0.9)	<0.05	0.63 (0.36-1.12)	0.119	0.98 (0.74-1.31)	0.915		
Perivascular invasion	2.36 (1.60-3.46)	<0.05	1.12 (0.68-1.86)	0.657	1.94 (1.42-2.67)	<0.05	1.16 (0.78-1.73)	0.463
Inflammatory carcinoma	2.98 (1.82-4.9)	<0.05	1.05 (0.56-1.98)	0.885	2.52 (1.66-3.81)	<0.05	1.43 (0.87-2.35)	0.156
Loco-regional extra axillary lymph nodes	0.71 (0.18-2.86)	0.627			1.06 (0.44-2.57)	0.896		
ITC	0.32 (0.04-2.26)	0.252			0.36 (0.09-1.46)	0.154		
Micrometastasis	1.20 (0.59-2.46)	0.610			0.97 (0.53-1.78)	0.930		
Extra-capsular invasion	6.90 (4.86-9.79)	<0.05	1.47 (0.83-2.62)	0.186	4.62 (3.42-6.24)	<0.05	1.31 (0.78-2.2)	0.306
Bunched lymph nodes	9.91 (6.7-14.68)	<0.05	2.16 (1.22-3.83)	<0.05	7.22 (5.03-10.37)	<0.05	2.3 (1.34-3.94)	<0.05
N>0	7.79 (5.1-11.88)	<0.05	1.35 (0.7-2.62)	0.369	4.34 (3.28-5.74)	<0.05	1.74 (1.1-2.75)	<0.05
TNM Stage III					5.51 (4.24-7.15)	<0.05	1.21 (0.7-2.07)	0.500
TNM Stage III-IV	11.08 (7.76-15.84)	<0.05	2.59 (1.29-5.17)	<0.05				

Stage III G3 tumors seemed even to have a significant advantage by conservative surgical treatment over breast demolition (Figures 1D and 1E). Considering G3 breast cancer in Table 5 it is shown that disease-free survival was influenced by: BCS, bunched axillary lymph nodes, and high Mib-1.

Discussion

In this study, the authors found that G3 breast cancers were associated with tumor characteristics, indicative of more aggressive behavior and with reduced overall- and disease-free survival. Although they were more frequently treated with demolitive surgery and chemotherapy, prognosis of G3 tumors at Stages I and II did not change in case of radical or conservative surgical treatment, while Stage III G3 tumors had a significant prognostic advantage by conservative surgery.

A possible explanation for this last result may be that G3 tumors, which are usually considered more aggressive, are consequently treated with more aggressive adjuvant and neoadjuvant therapies, and conservative surgery may be considered and achieved for patients with Stage III G3 cancers which attained a good response after neoadjuvant treatment. Obviously, while planning conservative surgery, it is of fundamental importance the evaluation of tumor size and location, as well as of breast volume, in order to guarantee the best aesthetic result.

In the current literature, the percentage of clinical responses to neoadjuvant therapies varies between 60% and 90% with a complete clinical response rate ranging between 6% and 65%, and the ability to carry out conservative surgery in candidates for mastectomy of about 20% to 30% [20, 21]. In a study, approximately 80% of women undergoing neoadjuvant therapies experienced a response to therapy with tumor reduction > 50% which led to a conservative treatment [22], and there is increasing evidence that a complete remission after neoadjuvant chemotherapy also impacts favorably on survival [23, 24]. Moreover, the best responses to neoadjuvant treatments are usually obtained in patients with less differentiated tumors (G3), with ductal histology, higher proliferation index (MIB1/Ki-67), and estrogen receptors negativity [25] and actually, in the present population, G3 tumors showed a significantly lower prevalence of estrogen receptors' expression and a signifi-

Table 5. — *Overall survival and disease free survival univariate (*) and multivariate (**) Cox analysis in G3 subgroup.*

	Overall survival				Disease free survival			
	HR (95% CI) (*)	*p* (*)	HR (95% CI) (**)	*p* (**)	HR (95% CI)	*p*	HR (95% CI)	*p*
BCS 0.41	(0.24-0.7)	<0.05	0.61 (0.31-1.19)	0.146	0.6 (0.4-0.89)	<0.05	0.57 (0.33-0.99)	<0.05
Age	1.02 (1-1.03)	0.076	1.03 (1-1.05)	<0.05	1 (0.99-1.02)	0.780		
Post-menopausal status	1.54 (0.84-2.82)	0.159			1.03 (0.65-1.61)	0.914		
Neoadjuvant chemotherapy	1.63 (0.91-2.92)	0.099	1.25 (0.66-2.4)	0.492	1.82 (1.13-2.93)	<0.05	1.56 (0.89-2.72)	0.120
Adjuvant radiotherapy	0.75 (0.48-1.19)	0.223	0.55 (0.32-0.94)	<0.05	1.49 (1-2.21)	0.051	1.39 (0.79-2.46)	0.252
Adjuvant chemotherapy	2.84 (1.56-5.18)	<0.05	2.31 (1.13-4.73)	<0.05	2.07 (1.33-3.21)	<0.05	1.54 (0.88-2.72)	0.133
Adjuvant hormonal therapy	0.52 (0.33-0.82)	<0.05	0.66 (0.36-1.21)	0.179	0.64 (0.44-0.93)	<0.05	0.63 (0.35-1.13)	0.118
Tumor histology								
Invasive ductal carcinoma	Reference	1.000			Reference	1.000		
Invasive lobular carcinoma	1.22 (0.49-3.05)	0.663			1.01 (0.44-2.3)	0.986		
Invasive ductal and lobular carcinoma	0.95 (0.38-2.37)	0.913			1.37 (0.71-2.63)	0.345		
Other invasive carcinoma	1.33 (0.48-3.66)	0.581			0 (0-Inf)	0.994		
Basal-like subtype	1.45 (0.88-2.41)	0.149	1.12 (0.56-2.21)	0.755	1.49 (0.98-2.28)	0.062	1.06 (0.56-2)	0.857
Positivity to Her2/neu	0.75 (0.42-1.32)	0.318			1.15 (0.74-1.77)	0.535		
Mib-1 >20	1.51 (0.83-2.75)	0.175			2.84 (1.58-5.11)	<0.05	1.87 (0.99-3.51)	0.054
Comedo-like necrosis	0.54 (0.25-1.17)	0.118			1.33 (0.83-2.12)	0.235		
Multifocality/multicentricity	1.09 (0.66-1.82)	0.733			1.29 (0.85-1.94)	0.233		
EIC	0.61 (0.37-1.02)	0.061	0.73 (0.41-1.29)	0.275	1.06 (0.72-1.56)	0.756		
Perivascular invasion	1.91 (1.19-3.07)	<0.05	1.17 (0.7-1.96)	0.551	1.28 (0.83-1.97)	0.256		
Inflammatory carcinoma	1.69 (0.89-3.2)	0.108	0.95 (0.47-1.95)	0.898	1.85 (1.11-3.11)	<0.05	1.36 (0.77-2.41)	0.293
Loco-regional extra axillary lymph nodes	0.9 (0.13-6.5)	0.919			2.00 (0.63-6.29)	0.238		
ITC	0.74 (0.1-5.34)	0.767			0.95 (0.24-3.86)	0.946		
Micrometastasis	1.41 (0.52-3.86)	0.503			1.01 (0.37-2.73)	0.990		
Extra-capsular invasion	4.45 (2.79-7.09)	<0.05	1.43 (0.77-2.66)	0.263	3.37 (2.23-5.09)	<0.05	1.47 (0.77-2.79)	0.243
Bunched lymph nodes	6.29 (3.79-10.44)	<0.05	1.67 (0.9-3.09)	0.104	4.96 (3.07-8)	<0.05	2.11 (1.1-4.03)	<0.05
N>0	4.24 (2.51-7.15)	<0.05	1.44 (0.69-2.99)	0.329	3.08 (2.07-4.59)	<0.05	1.56 (0.87-2.8)	0.132
TNM Stage III					3.61 (2.48-5.26)	<0.05	1.03 (0.5-2.13)	0.939
TNM Stage III-IV	7.33 (4.45-12.07)	<0.05	3.48 (1.64-7.41)	<0.05				

cantly higher proliferation index, both predictive factors for a better response to neoadjuvant therapies.

Taking into account the natural history and the biological behavior of breast cancer, there may be also another explanation for the favorable prognosis of Stage III G3 cancers who underwent conservative surgery. In fact, not all Stage III cancers are the same in terms of prognosis. In fact, it is not uncommon that large tumors that involve the skin or muscle (Stages IIIa and IIIb), or those that independently by the size present with a massive lymph node involvement (Stage IIIc), have a good prognosis and do not develop distant disease.

The appearance of a loco-regional recurrence of breast cancer consists in the clinical evidence of recurrent disease in the loco-regional lymph node stations and/or in the chest wall after radical surgery, or within the residual breast parenchyma after conservative surgery. The prognostic significance of loco-regional recurrences varies according to their size and location and the characteristics of aggressiveness of the primary tumor. A better prognosis is generally recognized for patients who undergo isolated intramammary recurrence (50-70% survival at five years), while in other cases relapse often preludes to the appearance of distant recurrences [25].

In the present population, Stage III G3 cancers showed a worse disease-free survival after mastectomy than after breast conservative surgery, and local recurrence after mastectomy had a significantly worse prognosis than those occurring after conservative surgery. Supporting the present result, the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials observed that patients with negative lymph nodes who underwent lumpectomy and adjuvant therapy had a low incidence of locoregional recurrences [25, 26] and in case of recurrence after conservative surgery, it is always possible to perform a salvage mastectomy, which the current literature demonstrates to achieve a similar prognosis than primary mastectomy [27, 28].

The strength of the present study is the great number of considered cancers, and the great reproducibility of breast cancer management in this setting, performed by the same pool of breast experts since 2002. The weakness is the retrospective design of the study, and surely prospective studies are required in order to better define overall- and disease-free survival after conservative *vs.* radical surgery for G3 breast cancers.

In conclusion, G3 breast cancers should be considered with particular attention to their aggressiveness when plan-

ning the therapeutic procedure. However, breast demolitive surgery should be carefully scheduled and reserved for women who cannot benefit from complementary therapies to conservative surgery. It is also mandatory to remember that breast cancer treatment should include a multidisciplinary management, in order to deal with all aspects of the treatment of breast cancer both before and after surgery.

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