

Article

Disease-Free Survival after Breast Conservation Therapy vs. Mastectomy of Patients with T1/2 Breast Cancer and No Lymph Node Metastases: Our Experience

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Abstract: Several retrospective analyses of large amounts of contemporary data have shown the superiority of breast conservative surgery (BCS) over mastectomy carried out in the early stage of breast cancer. The characteristics of the patients and cancers that are most likely to benefit from BCS remain unclear. In our work, we analyzed the disease-free survival (DFS) of a cohort of patients treated with BCS or mastectomy between 1995 and 2018 in our institute with pT1-2, pN0, or cM0 breast cancer. The DFS curves of patients treated with both mastectomy and quadrantectomy were compared in the different subsamples with respect to the clinical and histopathological characteristics. We identified 188 eligible patients treated with BCS and 64 patients treated with mastectomy. DFS was not found to be statistically higher in patients treated with BCS compared to those treated with mastectomy, who achieved a 5-year DFS of 89.9% vs. 81.3% and a 10-year DFS of 78.9% vs. 79.3%, respectively. No significant differences were detected for the DFS curves when patients were differentiated by the type of surgical treatment received, age, and the tumor histological characteristics. We verified a *p*-value just above the 10% significance threshold for patients with tumor dimensions between 20 mm and 50 mm and molecular sub-type Luminal B. In our experience, treatment with mastectomy is not associated with improved DFS compared to treatment with BCS in women with early-stage tumors.

Keywords: conservative breast surgery; mastectomy; quadrantectomy; breast cancer disease-free survival; early stage cancers; T1-2 tumors; N0 tumors

1. Introduction

Breast cancer surgery has undergone profound changes in the last few decades [1,2]. Breast conservative surgery (quadrantectomy, BCS) and the adoption of new techniques for “conservative” mastectomy (skin-sparing and nipple-sparing) are clear examples of oncological surgery aimed at improving the patient’s aesthetics and quality of life.

The most important studies that showed a substantial equivalence between BCS plus adjuvant radiotherapy of the entire breast and mastectomy were conducted some decades ago [3,4]. Their conclusions were crucial in changing the approach to local breast cancer treatment. Nevertheless, the scenario today has substantially changed. Nowadays, in this context, the preservation of the mammary organ by BCS has become the treatment of choice, thanks to the excellent results and optimal tolerability achieved [5,6]. However, various population-based studies have shown that mastectomy is still considered a reliable treatment option chosen by some breast cancer patients in daily clinical practice. The breast cancer survival rates are now higher. This is probably due to several factors, such as the smaller tumor dimensions, fewer patients with positive lymph nodes at diagnosis, as well as the more effective therapies available, including neoadjuvant therapies based on specific neoplastic characteristics [7,8].

In recent years, several retrospective analyses of large contemporary datasets have shown the superiority of treatment with BCS over treatment with mastectomy in the early stages of breast cancer. BCS was found to provide better outcomes than mastectomy for eligible patients with stage I breast cancer, in terms of specific survival and overall survival, and thus should be offered as a preferred treatment option [9–11]. Moreover, other studies focused on young women [12,13] and on triple-negative breast cancer [14,15] have shown similar results.

In some studies, locoregional recurrence percentages have been found to be higher after BCS than after mastectomy [16]. This has been further confirmed in triple-negative breast cancer and positive receptor 2 of the human epidermal growth factor (HER2) [15], even though Zumsteg et al. reported contradictory results [14]. Unfortunately, the locoregional recurrence percentages were rarely provided in the cited retrospective analyses, as the data were not always reliable. Therefore, the presumed superiority of mastectomy over BCS in reducing locoregional recurrence has not been clearly shown. Moreover, the subgroup of patients that could benefit from BCS remains unclear.

In this paper, we analyzed the disease-free survival of the patients treated in our institute, differentiating between patients who received breast conservative therapy and patients who received mastectomy. We studied evidence gathered for different subgroups of patients treated at our institute in the last 20 years.

2. Materials and Methods

2.1. Experimental Data

For this study, we considered women referred to the I.R.C.C.S. “Giovanni Paolo II” Cancer Institute (Bari, Italy) from 1995 to 2018. We collected data from 250 patients according to the following inclusion criteria: (i) female gender (ii) histologically confirmed invasive breast carcinoma; (iii) no metastatic ab initio cancer (pM0); (iv) negative lymph node status (pN0); (v) pT1-2 tumor size; (vi) patients who had received prophylactic mastectomy.

A clinically node-negative axilla was defined as no palpable lesion to suggest the spread of disease to the axilla and those who did not have suspicious signs in an axillary ultrasound.

Women who underwent mastectomy with T1-2 N0 stage did not receive adjuvant radiotherapy. On the contrary, women who underwent quadrantectomy received adjuvant radiotherapy on the remaining breast regardless of their stage [17].

This study was approved by the scientific board of our institute and carried out in the manner prescribed by the Helsinki declaration. All patients who gave consent to use the data for scientific purposes were recruited.

Several histological outcomes were recorded, including tumor size, tumor type, tumor grade G, multifocality/multicentricity, concomitant ductal carcinoma in situ (DCIS), estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor (HER2) status, Ki-67, the presence of lymphovascular invasion, and type of breast surgical procedure. Histological analyses were performed by the pathology department of our institute.

The expressions of ER, PR, and Ki-67 antigens associated with cell proliferation were valued in percentage terms. A cut off value of 20% positive cells was used to indicate tumors that were highly proliferating. HER2 status was considered to be positive if immunostaining was 3+ or if a score of 2+ showed gene amplification using fluorescence in situ hybridization (FISH).

The tumor histological grade G was defined by the Elston–Ellis modification of the Scarff–Bloom–Richardson grading system on a three-grade scale. Specifically, the duct structures, size and shape of the nucleus in the tumor cells, and mitotic rate were assessed. A lesion could be of grade G1 (low grade), G2 (intermediate grade), or G3 (high grade), where a lower grade indicated a better prognosis [18]. Moreover, we evaluated tumor size stage and lymph node stage according to the TNM staging classification system. Specifically, we considered only patients with a tumor of category T1 (<20 mm) or T2 (\geq 20 or <50 mm) in terms of size and negative lymph node status (N0).

2.2. Follow Up and Statistical Analysis

DFS was described as the timeframe between diagnosis and locoregional/distant relapse (second invasive breast cancer, second primary cancer, and/or death without evidence of breast cancer at the date of last contact).

The age of the patient at the first tumor event was described using medians and ranges. In order to evaluate the association between each clinical feature and the sentinel lymph node status, we used the Mann–Whitney test, whereas we used Fisher’s exact test for all of the other features that were measured on an ordinal and nominal scale.

DFS analyses of histological features were performed using the Kaplan–Meier method (5 and 10 years, 95% confidence interval (CI)) and compared by the log rank test.

The Hazard Ratio (HR) for univariate analyses was calculated by the Cox proportional hazard regression model.

All statistical analyses were performed using SPSS software version 25.0 (SPSS Inc, Chicago, IL, USA).

3. Results

Table 1 summarizes the characteristics of the examined sample. A total of 252 patients were examined, 188 of which (74.6%) underwent conservative surgery (quadrantectomy), while 64 patients (25.4%) underwent mastectomy. Among patients with breast cancer dimensions of less than 20 mm (T1 stage), the percentage of conservative surgeries was significantly higher than that of mastectomies (respectively, 71.81% and 53.13%, p -value Fisher’s exact test < 0.01). Moreover, 14.29% and 25% of the patients treated with conservative surgery and mastectomy, respectively, had a multifocal or multicenter tumor (p -value Fisher’s exact test < 0.05). No other significant differences were detected between the two considered groups (mastectomy vs. conservative surgery), even when the type of recurrence was considered.

No significant differences were detected in the disease-free survival (DSF) curves of mastectomy patients and conservative surgery patients (p -value Log–Rank test of 0.957) (Figure 1). The estimated 5-year and 10-year disease-free survival probabilities were 89.9% and 78.9%, respectively, for quadrantectomy patients, whereas they were 81.3% and 79.3%, respectively, for mastectomy patients. No significant differences were detected for the DFS curve differentiated by type of surgical treatment, age, or tumor histological characteristics, except for patients with tumor dimensions of between 20 mm and 50 mm and molecular sub-type Luminal B, where a significance level of 10% was considered (Table 2).

In reference to the Luminal B tumor patients, the estimated 5-year and 10-year disease-free survival probabilities were 88.1% and 77.8%, respectively, for mastectomy patients, whereas they were 58.8% (for both 5 years and 10 years) for quadrantectomy patients (Figure 2a). In reference to patients whose tumor dimensions ranged from 20 mm to 50 mm, the estimated 5-year and 10-year disease-free survival probabilities were 79.2%

and 71.2%, respectively, for quadrantectomy patients, whereas they were 83.3% and 79.7%, respectively, for mastectomy patients (Figure 2b).

Table 1. Characteristics of the total collected data ($n = 252$) as well as separate characteristics of patients treated with BCS ($n = 188$) and mastectomy ($n = 68$).

		BCS ($n = 188$)	(%)	Mastectomy ($n = 64$)	(%)	Total ($n = 252$)	(%)
Age at diagnosis	Mean (IC 95%)	54 (52–56)		54 (52–57)		54 (52–55)	
	≤54	108	57.4	31	48.4	113	44.8
	>54	80	42.5	33	51.6	139	55.2
	Total	188	100.00	64	100.00	252	100.00
ER	Neg	56	30.11	21	33.87	77	31.05
	Pos	130	69.89	41	66.13	171	68.95
	Total	186	100.00	62	100.00	248	100.00
PgR	Neg	62	33.51	25	40.32	87	35.22
	Pos	123	66.49	37	59.68	160	64.78
	Total	185	100.00	62	100.00	247	100.00
Ki67 ($\geq 20\%$)	Low	86	45.74	27	42.19	113	45.56
	High	98	52.13	37	57.81	135	54.44
	Total	188	100.00	64	100.00	248	100.00
HER2	Neg	136	85.53	48	84.21	184	85.19
	Pos	23	14.47	9	15.79	32	14.81
	Total	159	100.00	57	100.00	216	100.00
Molecular subtype	Luminal A	76	44.19	20	32.79	96	41.20
	Luminal B	42	24.42	17	27.87	59	25.32
	HER2 pos	23	13.37	15	24.59	38	16.31
	Triple negative	31	18.02	9	14.75	40	17.17
	Total	172	100.00	61	100.00	233	100.00
Histological Diagnosis	Ductal	168	89.36	53	82.81	221	87.70
	Other	20	10.64	11	17.19	31	12.3
	Total	188	100.00	64	100.00	252	100.00
Tumor size **	T1	135	71.81	34	53.13	169	67.06
	T2	53	28.19	30	46.88	83	32.94
	Total	188	100.00	64	100.00	252	100.00
Grading	G1	25	14.04	6	10.17	31	13.08
	G2	79	44.38	30	50.85	109	45.99
	G3	74	41.57	23	38.98	97	40.93
	Total	178	100.00	59	100.00	237	100.00
Multiplicity/Multifocality *	No	156	85.71	45	75.00	201	83.06
	Yes	26	14.29	15	25.00	41	16.94
	Total	182	100.00	60	100.00	242	100.00
DCIS	Absent	127	75.60	32	60.38	159	71.95
	Present	41	24.40	21	39.62	62	28.05
	Total	168	100.00	53	100.00	221	100.00
Type of shooting	Locoregional	20	33.33	3	15.79	23	29.11
	Other	40	66.67	16	84.21	56	70.89
	Total	60	100.00	19	100.00	79	100.00

* p -value Fisher's exact test < 0.05, ** p -value Fisher's exact test < 0.01.

Table 2. DFS and HR of patients treated with BCS and mastectomy with respect to age and histological characteristics. *p*-value refers to the DFS curve for the sub-sample considered. HR was calculated for each of the subcategories of patients with respect to the type of intervention received, considering BCS the reference category. ptz.: patients; Ev.: events; Pr.: probability.

		BCS						Mastectomy						<i>p</i> -Value	HR	<i>p</i> -Value
		ptz.	Ev.	5 Year DFS Pr. (95% CI)	Ev.	10 Year DFS Pr. (95% CI)	ptz.	Ev.	5 Year DFS Pr. (95% CI)	Ev.	10 Year DFS Pr. (95% CI)					
Age at disease	≤54	108	18	83.3 (74.9–89.8)	34	68.1 (85.9–77.1)	31	7	77.4 (58.9–90.4)	9	69.3 (48.6–83.3)	0.678	1.147 (0.594; 2.214)	0.683		
	>54	80	7	91.3 (82.8–96.4)	10	87.1 (78.2–93.8)	33	5	84.8 (64.5–93.0)	7	77.5 (61.1–91.0)	0.252	0.598 (0.244; 1.466)	0.261		
Molecular subtype	Luminal A	76	6	92.1 (83.6–97.1)	10	86.6 (77.1–93.5)	20	1	95.0 (75.1–99.9)	3	83.1 (62.1–96.8)	0.600	1.391 (0.401; 4.817)	0.603		
	Luminal B	42	5	88.1 (74.4–96.0)	9	77.8 (63.2–89.7)	17	7	58.8 (32.9–81.6)	7	58.8 (32.9–81.6)	0.091	0.474 (0.193; 1.162)	0.103		
	HER2 pos	23	5	78.3 (56.3–92.5)	10	54.9 (34.5–76.8)	15	3	66.7 (34.4–88.2)	3	66.7 (34.4–88.2)	0.758	1.279 (0.339; 4.823)	0.717		
	Triple negtive	31	3	90.3 (74.3–98.0)	9	71.0 (52.0–85.8)	9	1	93.3 (51.8–99.7)	2	84.8 (40.0–97.2)	0.522	1.220 (0.339; 4.390)	0.761		
Histological diagnosis	Ductal	168	23	86.3 (79.5–90.6)	40	75.6 (68.4–81.9)	53	11	79.2 (65.9–89.2)	14	72.0 (57.7–83.2)	0.707	0.902 (0.523; 1.557)	0.902		
	Other	20	2	90.0 (68.3–98.8)	4	79.4 (56.3–94.3)	11	1	90.9 (58.7–99.8)	2	80.8 (39.0–94.0)	0.438	1.971 (0.343; 11.326)	0.447		
Tumor size	T1	135	10	93.3 (87.7–96.9)	29	77.9 (69.8–84.5)	34	7	79.4 (62.1–91.3)	10	66.9 (49.5–82.6)	0.187	0.649 (0.338; 1.248)	0.195		
	T2	53	11	79.2 (65.9–89.2)	15	71.5 (57.7–83.2)	30	5	83.3 (65.3–94.4)	6	79.7 (61.4–92.3)	0.099	2.012 (0.856; 4.725)	0.109		
Grading	G1	25	0	100 (86.9–100)	1	95.8 (76.7–99.9)	6	0	100 (54.1–100)	1	83.3 (35.9–99.6)	0.735	0.668 (0.077; 6.156)	0.738		
	G2	79	9	88.6 (79.5–94.7)	17	77.9 (66.4–85.9)	30	6	80.0 (61.4–92.3)	9	65.9 (47.2–82.7)	0.167	0.599 (0.285; 1.259)	0.176		
	G3	74	14	81.1 (86.7–98.5)	23	68.1 (55.7–78.0)	23	6	73.9 (51.6–89.8)	6	73.9 (51.6–89.8)	0.476	1.368 (0.568; 3.298)	0.485		
Multiplicity/Multifocality	No	156	22	85.9 (79.4–91.0)	37	74.9 (67.5–81.9)	45	6	86.7 (73.2–95.0)	8	80.9 (65.4–90.4)	0.329	1.376 (0.717; 2.644)	0.337		
	Yes	26	3	88.5 (69.9–97.6)	6	76.6 (52.2–88.4)	15	5	66.7 (38.4–88.2)	7	51.9 (26.6–78.7)	0.123	0.449 (0.156; 1.297)	0.139		
DCIS	Absent	127	16	87.4 (80.4–92.6)	27	78.4 (70.6–85.5)	32	3	90.6 (75.0–98.0)	5	83.4 (67.2–97.7)	0.402	1.408 (0.624; 3.176)	0.410		
	Present	41	5	82.9 (67.9–92.9)	11	61.5 (44.5–75.8)	21	5	66.7 (43.0–85.4)	5	66.7 (43.0–85.4)	0.940	0.829 (0.354; 1.941)	0.666		
Type of shooting	Locoregional	20	5	95.9 (75.1–99.9)	13	90.9 (68.3–98.8)	3	2	95.8 (30.0–100)	2	95.8 (30.0–100)	0.151	2.363 (0.702; 7.954)	0.165		
	Other	40	20	88.1 (73.2–95.8)	32	80.6 (64.4–91.0)	42	10	83.6 (68.6–93.0)	14	75.4 (34.7–93.3)	0.563	0.844 (0.471; 1.511)	0.567		

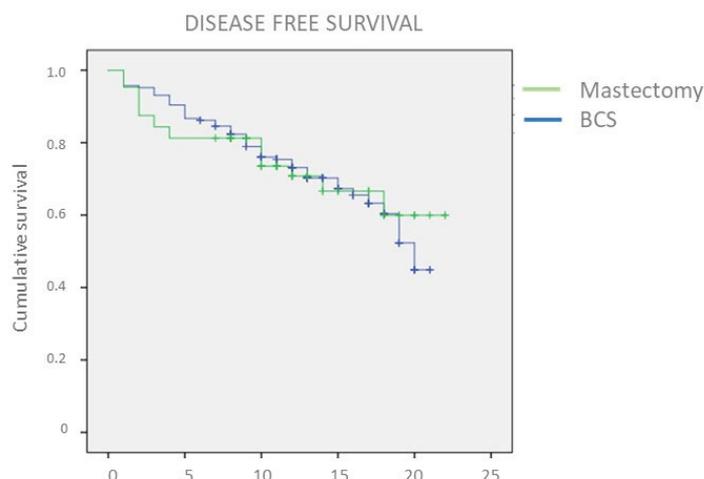


Figure 1. Disease-free survival curve according to type of surgical treatment received.

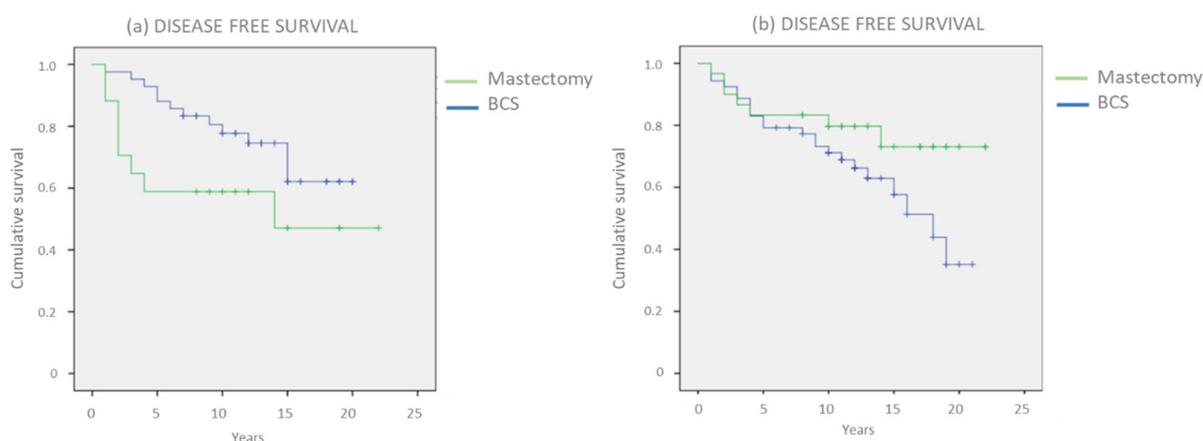


Figure 2. Disease-free survival curve for patients with Luminal B tumor type (a) or a tumor size between 20 mm and 50 mm (b) according to type of surgery received.

There were no significant differences in survival curves for BCS patients and mastectomy patients in each of the considered histological characteristics subgroups. No differences were detected even when the patient's age at first diagnosis was considered (Table 2). The only exception was for tumor dimensions ranging from 20 mm to 50 mm as well as for Luminal B tumors. In these cases, a significant difference close to the acceptable threshold of 10% was detected (p -values of 0.109 and 0.103, respectively). In more detail, it seemed that in T2 tumor patients, the recurrence probability could rise by 101.2% in BCS-treated patients compared to mastectomy-treated patients (HR = 2.102). The same probability of recurrence seemed to be reduced by 63.6% in the case of the Luminal B tumor patients (HR = 0.474).

4. Discussion

The introduction of the onco-plastic approach in breast surgery by means of quadrantectomy and "conservative" mastectomy techniques [19], when possible, is an emblematic example of the need for an increasingly targeted, personalized, and multidisciplinary treatment. In fact, treatment should consider the oncological radicality, personal risk, satisfaction, and quality of life of the patients [20,21], guaranteeing as much as possible both an effective treatment in terms of oncological radicality and acceptable aesthetic results, as well as minimizing the negative psychological impact of mastectomy through skin-sparing and nipple-sparing.

Recent large-scale studies have shown that patients treated with BCS followed by radiotherapy have had better outcomes than those treated with radical mastectomy alone [11,16]. Specifically, significantly better outcomes were achieved for local relapses, distant metastases, and overall survival when using the conservative approach.

From this point of view, patients with a high-risk family history or a confirmed genetic mutation deserve to be discussed separately. Although most tumors are sporadic, a non-insignificant percentage of mammary tumors (5–10%) are, in fact, linked to hereditary factors [22]. More than 2/3 of these result from a mutation of the BRCA-1 and 2 genes, whose presence exposes the patient to the risk of developing mammary and/or ovarian neoplasms in the course of their life in 61–79% and 11–53% of cases, respectively [22,23]. This is especially the case in patients with a BRCA-1 mutation, who may develop peculiarly highly aggressive triple-negative tumors (ER-/PgR-/HER2-), often with lymph node metastases at the first diagnosis and with a higher rate of long-term relapse [24–26].

Similarly, the real impact on patient survival in the case of prophylactic mastectomy is uncertain, particularly in non-sick women with mutated BRCA, although this practice reduces the possibility of disease onset in over 90% of cases [27–30]. However, some studies have shown a significant reduction in mortality in women who have already been operated on for breast cancer [27]. These types of patients, on whom there is also an indication for the prophylactic mastectomy of both breasts, were excluded from our study, as they would have constituted a bias of the study itself.

In our experience, there are no significant differences in terms of disease-free survival between patients treated with mastectomy and those treated with BCS, particularly at 10 years, even when differentiating by age and histological characteristics. On the other hand, at 5 years, the relative difference in survival in favor of quadrantectomy (89.9% vs. 81.3%) may be a consequence of the greater share of advanced tumors in patients who received a mastectomy and their consequent higher rate of death in the first few years after this type of treatment.

Considering a significance level of 10%, a statistical difference is observed with reference to the disease-free survival of patients with Luminal B tumors and with tumor sizes between 20 mm and 50 mm. In the latter case, the best result of mastectomy is achieved at 5 years, but at 10 years this could be linked to the criterion of greater surgical radicality, especially in large or multiple tumors.

We have attempted to explain the data relating to the reduced survival seen in patients with Luminal B tumors treated with mastectomy compared to those treated with quadrantectomy. This could have been due to the detection of a greater number of single bone metastases in patients with Luminal B breast cancer [31] compared to patients in the non-luminal groups, potentiated by the higher frequency of large and multicentric neoplasms present in mastectomies.

Although the locoregional recurrence seen in patients treated with mastectomy in our sample is too small to allow us to perform statistical evaluations, there does not seem to be a statistically significant difference between the patients treated with BCS and those treated with mastectomies.

Despite some limitations related to the sample size used in our study, our results are in line with those of well-known studies carried out on a larger scale. Future studies should include an analysis of overall survival by evaluating additional factors of interest and differentiating DFS between BCS patients with positive margins and a mastectomy group.

5. Conclusions

In our study, we found no statistically significant differences in terms of disease-free survival between patients who received mastectomy and patients treated with breast conservative surgery (BCS), even when differentiating by age and histological characteristics. A statistically significant difference was observed in patients with Luminal type B tumors and with a tumor size between 20 mm and 50 mm (T2), where a significance level of 10% was considered. The refinement of the diagnosis, which has been made possible through the

cutting-edge techniques of fusion of images, radiomics, and artificial intelligence [32–37], could contribute to an earlier detection of neoplasms and, therefore, to a more conservative surgical approach being used.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data presented in this study are available on request from the corresponding author. The data are not publicly available because they are propriety of Istituto Tumori ‘Giovanni Paolo II’—Bari, Italy.

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