

Applicability of the Nottingham Prognostic Index for predicting the survival of triple-negative invasive breast cancer in a single Italian center

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Summary

Objective: Triple-negative breast cancer (TNBC) is recognized to have a very poor prognosis due to its strong tendency to develop distant metastases. The present study aims to evaluate the applicability of the Nottingham Prognostic Index (NPI) in women affected or not by invasive TNBC in our centre. **Materials and Methods:** A retrospective study on women operated in the authors' Department for invasive breast cancer between January 2002 and January 2007 was carried out, with a follow up of at least five years. Patients were divided into three groups based on the three prognostic categories of NPI and every category was again subdivided in TNBC or non-TNBC. Data was collected about tumor histology and biological assessment, patients characteristics, treatment, and follow up in terms of overall survival (OS). **Results:** The authors included 917 women operated for invasive breast cancer during this period, at a mean age of 61.4 ± 12.58 years. TNBC prevalence was 8% (71/917). Among the NPI classes, they found respectively a five- and eight-years' OS of 99% (98-100%) and 97% (95-98%) in group 1, 88% (83-93%) and 83% (77-89%) in group 2, and 69% (59-80%) and 55% (44-70%) in group 3 ($p < 0.05$). After stratification of every NPI group between TNBC and non-TNBC, they found a five-years' OS in TNBC and non-TNBC strata of respectively 94% (87-100%) and 99% (98-100%) in group 1 ($p < 0.05$), 85% (71-100%) and 89% (84-94%) in group 2 ($p = 0.834$), and 47% (26-85%) and 73% (63-85%) in group 3 ($p < 0.05$). **Conclusions:** NPI resulted as a very simple and valuable prognostic tool and TNBC, when associated with NPI groups, significantly modified the prognostic value of NPI itself.

Key words: Margins; Resection margins; Surgical margins; Breast cancer; Breast conserving surgery; Recurrence.

Introduction

The modern management of breast cancer cannot leave aside an accurate evaluation of the patient's individual prognosis, in order to better tailor adjuvant and eventually neoadjuvant therapies, and to better plan the surgical strategy [1–4]. In this perspective, many classifications have been created, such as the TNM staging system, which include the strongest prognostic factors for patients survival, with the aim to define breast cancer prognosis.

The Nottingham Prognostic Index (NPI) was first introduced in 1982, and subsequent studies demonstrated its good prognostic value at 15 years' follow up [5, 6]. In particular, it allows to identify three prognostic categories: a score values of less than 3.4 gives a good prognosis (85% OS at 15 years) (group 1), between 3.41-5.4 a moderate prognosis (42% OS at 15 years) (group 2), and more than 5.4 a poor prognosis (13% OS at 15 years) (group 3).

The triple-negative breast cancer (TNBC) phenotype seems to rely on different pathways in respect to non-TNBC phenotypes to spread at distant sites. In particular TNBC seems to prefer haematologic spread than a lymphatic one, frequently sparing the loco-regional lymph

nodes, while metastasizing to distant solid organs with a consequent poor prognosis [7–9].

This characteristic dissemination is not considered by NPI tool, so that this could limit its reliability in this particular subtype of invasive breast cancer. Therefore, the current study aims to evaluate the applicability of NPI in women affected or not by invasive TNBC cancer in the present centre, and to determine if the addition of TNBC could play a role in improving the NPI long time prognostic value.

Materials and Methods

A retrospective study was carried out on women operated in our Department for invasive breast carcinoma between January 2002 and January 2007, with a follow up of at least five years. The study was done according to the Declaration of Helsinki and it was approved by the local ethics committee. Moreover, regarding the consent for processing data used in this retrospective analysis, the authors followed the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority.

In this study the authors included all cases of invasive breast carcinoma that had full information about TNM stage, tumor grad-

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ing, hormonal status, and Her2/neu expression. Information for selection and analyses were gathered from the operative theater register and clinical files of this Clinic.

The main considered outcome in this study was overall survival (OS). Data about patient characteristics were collected as follows: body mass index (BMI), age at diagnosis, fertility status, familial history for breast or ovary cancer, and eventual use of estroprogestinic therapies. Considered tumor characteristics included: TNM tumor size, histological type, stage at diagnosis, Mib1/Ki-67 proliferation index, nuclear grading, hormone receptor status including estrogen receptor (ER), progesterone receptor (PR) and Her2/neu expression, and other microscopic features such as peritumoral inflammation (PTI), multicentricity/multifocality, perivascular invasion (PVI), or extensive intraductal component (EIC) [10]. Loco-regional lymph node characteristics were considered as follows: TNM nodal status, eventual involvement of loco-regional extra-axillary lymph nodes (internal mammary chain or subclavian ones), lymph node extracapsular invasion (ExCp), and bunched lymph nodes [3, 4, 11–14]. The authors also investigated the therapeutic management, taking into consideration eventual neoadjuvant therapies, breast and axillary surgery, and adjuvant treatment (breast irradiation, endocrine therapy, chemotherapy).

As previously described, tumor stage was defined according to the VII edition of the TNM classification (AJCC/UICC), tumor histology was classified according to the World Health Organization criteria as modified by Rosen and Oberman, and tumor grade was evaluated following the recommendations of Elston and Ellis [15]. The authors considered the presence of PVI according to Rosen and Oberman criteria as previously stated [15]. Furthermore, the expression and quantification of ER, PR, Her-2/Neu, and the tumor proliferative fraction (Mib1/Ki-67) were evaluated as previously described [15]. In addition, they defined the lymph node ExCp as the extracapsular growth of tumor cells, invasion of perinodal fat, or extranodal location of tumor cells [15]. For the purpose of this study, patients were then divided into three groups based on the three prognostic categories of NPI and every category was again subdivided between TNBC and non-TNBC.

Data was analyzed using R (version 3.1.0) and considering significant $p < 0.05$. Univariate analysis was performed by chi-square test or Fisher exact test in case of categorical variables, t -test in case of continuous parametric variables or Wilcoxon test in case of non-parametric ones. Kaplan-Meier curves were drawn to compare OS and DFS among the studied groups. Log-rank test was performed to assess differences in survival. In addition, the univariate and multivariate Cox proportional hazards regression model was also used to assess OS and correct possible confounding factors.

Results

The authors included in this study 917 women operated for invasive breast cancer during the considered period, and followed up for a mean time of 78.78 ± 31.21 months. In Table 1 they report patients' characteristics. The mean age at intervention was 61.4 ± 12.58 years, and the mean BMI was 25.36 ± 4.79 kg/m². In 30% (52/175) of cases a familial history of breast or ovarian cancer was reported. The majority of the population was in menopause (82%, 642/781), 30% of patients (52/175) assumed estrogenic therapies, and 6% (43/748) used to smoke tobacco.

In Table 2 the authors show tumor characteristics of the population. The most common histological type was ductal

Table 1. — *Population characteristics.*

Age (years)	61.4 (± 12.58)
BMI (kg/m ²)	25.36 (± 4.79)
Mean follow-up (months)	78.78 (± 31.21)
Mean follow-up to recurrence (months)	76.5 (± 29.2)
Tobacco smoke	6% (43/748)
Familial history of cancer	30% (52/185)
Estrogens assumption	30% (52/175)
Post-menopausal status	82% (642/781)
Non surgical treatment	
Neoadjuvant chemotherapy	7% (65/917)
Radiotherapy	59% (545/917)
Chemotherapy	42% (388/917)
Hormonal therapy	76% (694/917)

Table 2. — *Tumor characteristics.*

Histology	
Ductal invasive carcinoma	72% (662/917)
Lobular invasive carcinoma	14% (127/917)
Ductal and lobular invasive carcinoma	10% (91/917)
Other invasive carcinoma	3% (31/917)
Ductal in situ carcinoma	1% (6/917)
T stage	
Tis	1% (6/917)
T1	67% (618/917)
T2	25% (229/917)
T3	2% (18/917)
T4	5% (47/917)
N stage	
N0	62% (568/917)
N1	22% (203/917)
N2	7% (60/917)
N3	9% (86/917)
Locoregional non axillary lymph nodes	3% (24/917)
Tumor grading	
G1	7% (63/917)
G2	65% (597/917)
G3	28% (257/917)
Other tumor characteristics	
ER	84% (773/917)
PgR	74% (682/917)
HER2/new expression	10% (90/917)
Triple negative subtype	8% (71/917)
Mib1/Ki-67 > 20%	32% (297/917)
Comedo-like necrosis	8% (70/917)
Multifocality/multicentricity	28% (253/917)
EIC	28% (259/917)
PVI	7% (65/917)
PTI	8% (74/917)
Other lymph node characteristics	
Isolated tumor cells	3% (29/917)
Micrometastasis	5% (50/917)
Extracapsular invasion	9% (85/917)
Bunched lymph nodes	7% (64/917)

invasive carcinoma in 72% of cases (661/917) and the most frequent TMN stage was Stage I, with a significantly higher prevalence of tumor sized less than 2 cm, without any

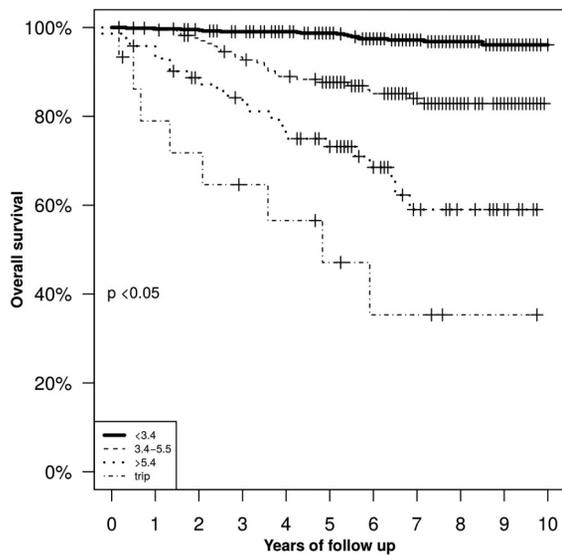


Figure 1. — Overall survival in triple negative breast cancers and other cancers (subdivided by NPI value).

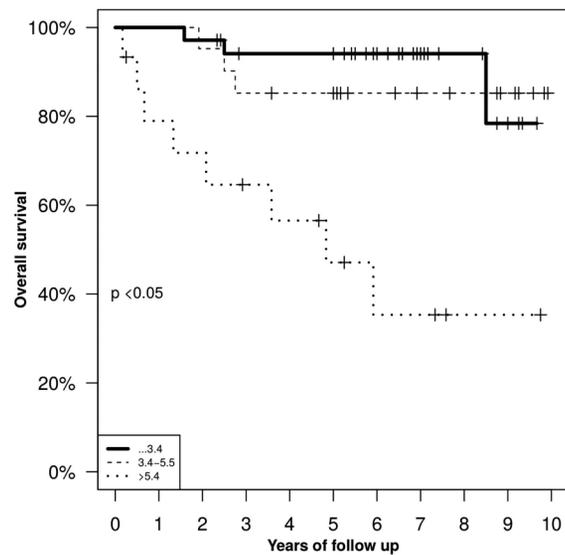


Figure 2. — NPI performance in triple negative breast cancers.

lymph node involvement or distant metastasis. Tumor grading was more frequently intermediate (65%), hormone receptors were expressed in the majority of cases (84% for estrogen and 74% for progesterone), and Her2/neu resulted expressed in only 10% of cases. TNBC prevalence was 8% (71/917). Figure 1 shows the overall survival of the study population divided into the three groups based on the NPI score. The authors found respectively a five- and eight-years' OS of 99% (98-100%) and 97% (95-98%) in group 1, 88% (83-93%) and 83% (77-89%) in group 2, and 69% (59-80%) and 55% (44-70%) in group 3 ($p < 0.05$). Thereafter, Figure 2 shows OS among the three NPI groups, including only TNBC. The authors found a five-years' OS, respectively, in TNBC and non-TNBC strata of 94% (87-100%) and 99% (98-100%) in group 1 ($p < 0.05$), 85% (71-100%) and 89% (84-94%) in group 2 ($p = 0.834$), 47% (26-85%) and 73% (63-85%) in group 3 ($p < 0.05$).

Discussion

In the present study population, the authors found TNBC to have a prevalence of 8%. OS was significantly different among the three NPI groups both taking into consideration the entire population or only triple-negative cancers.

The strengths of this study are the population size and the accurate and complete data collection, which allowed an adequate data elaboration. On the other hand, its weakness is without any doubt its retrospective design.

Despite the increase of early breast cancers diagnosed through the mammographic screening programs in this local setting [11, 16], there is still a group of patients whose prognosis does not exclusively depend on the tumor stage

at diagnosis, but unfortunately on some other molecular markers which are expression of the cancer biological behavior. For example, recently some molecular subtypes have been described by the literature, which take into consideration hormonal receptors status, Her2/neu expression and Mib1/Ki-67 proliferation index, and strongly correlate with breast cancer prognosis [17–19]. TNBC also defined as basal-like for its poor differentiation grade, results to have the worst prognosis among these subtypes, probably due to its trend to spread via bloodstream and consequently to develop distant metastasis [8, 20].

Usually, the many prognostic tools purposed by the literature during the last decades do not take into consideration the recent breast cancer classification among molecular subtypes, as they do not include the evaluation of hormonal receptors status or Her2/neu expression. Therefore, some simple prognostic tools such the NPI, which takes into consideration only tumor size, nodal status, and nuclear grading, could be somewhat deficient by predicting breast cancer prognosis. Especially in case of triple-negative cancer, the application of NPI results very controversial, because TNBC is associated with high grading in the great majority of cases and is infrequently disseminate to axillary lymph nodes. However, in this study the authors demonstrated that even an old and simple tool such as NPI could accurately predict breast cancer prognosis independently by the molecular subtype. In fact, the OS differences among the three NPI groups resulted to be significant, while considering both the entire population or only TNBC. The results are also in accordance with those of other authors who demonstrated NPI to be a truthful prognostic tool even in TNBC [21–23].

Recently, a new version of NPI has been introduced, called Nottingham Prognostic Index Plus (NIP+), which takes into account also biomolecular markers and thus supports an improved individualized clinical decision-making [24, 25]. Nonetheless, the study of Kurshumliu *et al.* confirmed that the original, three-tiered NPI statistically correlated with the expression of prognostic immunohistochemical markers in non-special type breast carcinoma [25]. In particular, they observed that the expression of markers of good prognosis, such as hormonal receptors expression, are more frequently present in case of good and moderate NPI groups, whereas markers of adverse prognosis, such as Her2/neu overexpression and high Mib1/ki-67 proliferation index, are more prevalent in the poor NPI group.

In summary, NPI resulted a valuable prognostic tool for the prediction of breast cancer overall survival in our local setting, even in case of triple-negative invasive breast cancers. In our opinion, it is important to associate this kind of tool with other more advanced biomolecular investigations in order to better evaluate triple-negative tumors, and to offer to such women the best surgical and non-surgical treatment as possible.

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