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Level of education, background and clinical stage as prognostic factors according to RMST function in patients with early and locally advanced breast cancer: a single institution experience from Romania

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Abstract

Background and aims. Our aim is to examine the relationship between the level of education, background, tumor size and lymph node status on the treatment outcome in a group of patients with early and locally advanced breast cancer (BC) by using the restricted mean survival time (RMST), which summarizes treatment effects in terms of event-free time over a fixed period of time.

Methods. We evaluated the prognostic values in 143 patients treated for early BC at Elias University Emergency Hospital, Bucharest, Romania and followed up for a maximum of 36 months. The protocol was amended to include the levels of education (gymnasium, high school, or university), the background (urban or rural) and the clinical stage (primary tumor (T) and regional nodes (N)). The methodology consisted in using a Kaplan–Meier analysis and RMST for the entire sample and Cox regression, for the variables with statistical influence. The principal endpoints of the study were overall survival (OS) and progression free survival (PFS).

Results. The level of education had impact both on RMST OS (35.30 vs. 26.70) and death HR (hazard ratio) in the group of patients with general school level, compared with those with graduated university. In this study, the urban or rural background did not impact the outcome, probably because in this study we included predominantly patients from urban areas (83%). Although clinical tumor size measurements did not impact the outcome, the clinical staged lymph node influenced both OS ($p=0.0500$) and PFS ($p=0.0006$) for the patients with palpable or imaging proof of lymph node involvement of station 2 or 3.

Conclusions. RMST provides an intuitive and explicit way to express the effect of those risk factors on OS and PFS in a cohort of early breast cancer patients. Low level of education and high-grade clinical lymph node status negatively influences the outcome of this cohort of BC patients.

Keywords: breast cancer, clinical stage, background, levels of education, RMST

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Introduction

BC is a major public health issue worldwide, with high mortality despite all the progression of screening and treatment procedures. Available data suggest that incidence and mortality in high-resource countries has been declining, whereas incidence and mortality in low-resource countries has been increasing. Reasons for the decline in mortality in the developed countries include widespread mammography screening, precise diagnosis and increased numbers of women receiving the best treatment for their conditions [1,2].

Only around 50% of mammary carcinoma can be attributed to known risk factors such as obesity, age at menarche, first live birth, or menopause. Another 10% are associated with positive family history. Those risk factors may be modified by demographic, lifestyle and environmental factors, and the association with the development of BC is unclear. Additionally, new risk factors have been studied, including psychological stress, smoking and nutrition, their management and exclusion possible offering great benefit [3,4].

Many risk factors associated with breast cancer cannot be changed, but some can be modified. The presence of breast cancer risk factors does not mean that cancer is inevitable; many women with risk factors never develop breast cancer. Instead, risk factors help identify women who may benefit most from screening or other preventive measures. Women should work with their clinicians to determine their own personal risk of breast cancer based upon their own circumstances [5-8].

Extensive research has taken place for subtyping breast cancer at molecular and genetic level and to determine various clinical, pathological, and molecular factors for the selection of treatment modalities and disease prognosis at the time of diagnosis. All efforts are made to identify influential risk factors and subsequently, even after the onset of cancer disease, are aimed to reduce BC mortality [9].

The World Health Organization defined the social determinants of health as the “conditions in which people are born, grow, work, live and age, and the wider set of forces and systems shaping the conditions of daily life” [10].

Social determinants of health that have been examined in relation to BC incidence, stage at diagnosis and survival include socioeconomic status (income, education), neighborhood disadvantage, unemployment, racial discrimination, social support, and social network. Other social determinants of health include medical distrust, immigration, status, inadequate housing, food insecurity and geographic factors such as neighborhood access to health services [11].

Socioeconomic factors may influence risk of BC. Low socioeconomic status is associated with increased risk of aggressive premenopausal BC, as well as late stage of

diagnosis and poorer survival. There are well-documented disparities in BC survival by socioeconomic status, race, education, census-tract-level poverty, and access to health insurance and preventive care. Poverty is associated with other factors related to late stage of BC diagnosis and poorer survival such as inadequate health insurance, lack of a primary care physician and poor access to health care [12,13].

BC is treated with a multidisciplinary approach involving anatomic pathology, surgical oncology, radiation oncology and medical oncology, which has been associated with a reduction in breast cancer mortality [14].

Levels of education and background

Throughout the world, there exists a disparity in breast cancer survival based on the median income of each country and to quantify this aspect the “Human Development Index” was developed. This is a measure of national well-being calculated from average life expectancy, the mean of schooling years and the gross national income per capita. Studies have shown that the mortality-to-incidence ratio of breast cancer was found to be significantly lower in countries with a very high human development index compared to those with high-, medium- and low-human development indices [15].

The levels of education of patients can be an important aspect in order to mitigate the risk factors and also through the regular use of screening methods addressed to each disease. It has been under discussion about twenty years ago, when the Cancer and Leukemia Group B (CALGB), a national cooperative group funded by the National Cancer Institute explored the relationship between socioeconomic status and survival of cancer patients enrolled in eight CALGB studies. After adjustment of known prognostic factors, including cancer type, performance status, age, analyses showed that clinical trial participants with low income or only a grade school education had poorer survival rate than patients with higher socioeconomic status [16].

As defined by the Institute of Medicine the social environment may influence health behavior by, “shaping norms, enforcing patterns of social control, providing or not providing environmental opportunities to engage in particular behaviors, reducing or producing stress, and placing constraints on individual choice” [17].

The background can represent a risk factor, considering the geographical area, but also the accessibility to a medical system. Living in an area without the possibility of employment, insecure from the military point of view, crowded or with poor living conditions may contribute to a state of chronic psychosocial stress. Also, the presence of ionizing radiation in the environment, to which survivors of atomic bomb or nuclear plant accidents are submitted, is associated with an increased risk of breast cancer [2,18-20].

The relation between socioeconomic status and levels of education has been a topic of research during the

last years. In his studies, Marmot argues that education may be a better indicator for factors linked to social position that are important to health and survival, given that the effect of income on mortality is markedly reduced when education is included in predictive models [21,22].

Clinical stage

The Tumor, Node, Metastasis (TNM) staging system for breast cancer is an internationally accepted system used to determine the disease staging. The primary tumor, lymph node and metastasis (TNM) classification staging system was first published in 1959 by the American Joint Commission of Cancer (AJCC). Since then, it has been regularly updated, with the seventh edition published in 2009. A new version, the eighth edition of the TNM classification, was revised and published in 2017 [23,24].

This disease staging is used to determine prognosis and guide management. It is also used to facilitate discussions about treatment and prognosis between collaborating providers, as well as between providers and patients. For BC, to assess the T category the clinicians have to evaluate both the tumor dimensions and the clinical aspect of the breast (e.g., extension to the chest wall, ulceration/ edema, inflammatory breast carcinoma) together with the N status. The clinical staging is assigned based on physical examination and imaging studies, while the pathological stage is assigned after surgery [25].

To establish the stage of a breast cancer, the first step is to evaluate the size of the tumor and establish whether the lymph nodes are metastatic or free of disease. For a definitive clinical diagnosis, the clinicians could use in addition to the clinical examination the data obtained from the mammogram examination or other imaging techniques (ultrasound or magnetic resonance imaging).

The correlation between primary tumor size and the likelihood of metastasis is based on the theory that, as a cancer grows, cells within the tumor acquire the capability to spread, survive and flourish within the regional lymph nodes and other distant sites. Most studies to date which have reported a correlation between primary tumour size and the likelihood of metastasis (to the lymph nodes or to distant sites) have treated all tumours smaller than 1.0 cm at diagnosis as a single category and those tumours larger than 5.0 cm at diagnosis as another category. There is a clear and consistent linear relationship between size and metastases in the size range between 1.0 and 5.0 cm, and it is assumed this curve can be extrapolated in both directions to predict the proportions of patients with nodal or distant metastases for very small and for very large tumours [26-29].

The patients with nonmetastatic breast cancer are divided into two categories according to the T and N stage: [30]

- Early stage: patients with stage I, stage IIA, or a subset of stage IIB disease (T2N1).
- Locally advanced: patients with stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease.

This study aimed to use our institutional data of breast cancer patients without metastases in order to identify how the environment of origin, the level of education and the clinical classification for tumor and lymph node may impact the survival of patients. We present here a detailed descriptive, retrospective study of the relationship between the background, level of education, clinical T, N stage and OS and PFS.

Methods

We conducted a retrospective, observational study on a early and locally advanced breast cancer patient cohort treated in Elias Emergency Hospital Bucharest, Romania, between January 2014 and December 2019. Our research was carried out with the approval and in accordance with the guidelines of the local Ethics Committee. All the procedures in the study respect the ethical standards in the Helsinki Declaration, and the protocol was approved by the Ethics Committee with the code 7423/2018.

One hundred and forty-three (143) patients newly diagnosed with breast cancer were recruited in our hospital and included in our study.

The **inclusion criteria** were: patients diagnosed with invasive breast carcinoma stages I, II, or III who received treatment in our hospital and which were followed-up for 36 month, 18 years age or older, Eastern Cooperative Oncology Group status of 0 or 1, absence of cardiac, pulmonary or hepatic comorbidities, unilateral breast tumor, absence of pregnancy in the last 6 months, absence of another associated type of neoplasia the study period and patients for whom were available all the data necessary to complete the database.

The **exclusion criteria** were: patients for whom the information corresponding to the variables described bellow were not available, the presence of a second concomitant cancer or the appearance of a neoplastic disease during the follow-up period, inoperable tumors before or after neoadjuvant therapy, the presence of metastatic disease at diagnosis, patients during lactation or weaning earlier than 6 months until the time of diagnosis.

For the background analysis, we divided the patients into two groups, taking into account the residence for the last 10 years, urban or rural respectively, in accordance with the current legislation [31].

The levels of education were appreciated according to the main school stages applied on the Romanian territory: the general school (level I), high school (level II) or higher education represented by the university (level III).

Clinical staging was performed before receiving any oncologic treatment and according to the clinical TNM stage at the time of diagnosis. Tumor size refers to the greatest dimension (usually the diameter) of the largest contiguous area of clinical palpable tumor. For non-palpable tumors the classification was performed using the tumor dimensions

provided by imaging examinations. Staging of the lymph nodes was based on either clinical or imaging findings (ultrasound or MRI). The proportion of patients with at least one positive regional lymph node metastasis was classified with positive nodes (AJCC classifications N1, N2 or N3). Patients classified as NX (nodes not assessed) were excluded from this analysis. Ultrasound axillary imaging included the evaluation of ipsilateral axillary lymph nodes level I (nodes lateral and inferior to pectoralis minor muscle and includes intramammary nodes) and II (nodes deep and posterior to pectoralis minor muscle and includes central and interpectoral nodes). We considered suspicious nodes the ones with the following findings: focal cortical bulging or eccentric cortical thickening, rounded hypoechoic lymph nodes, complete or partial effacement of the fatty hilum, and complete or partial replacement of lymph nodes with an ill-defined or irregular mass.

In addition to clinical examination, chest computed tomography (CT) and/or positron emission tomography and computed tomography, (PET/CT), if performed for distant evaluation were used for assessing level III and interpectoral nodes, as well as extensive nodal involvement in patients with advanced breast disease.

Although the recommendations of the guidelines indicate the percutaneous biopsy of for suspicious nodes, in our country this investigation can be performed only in some centers and is not used routinely. In this study, pathological confirmation for the suspicious nodes was not performed. After the cancer confirmation, the patients received chemotherapy or hormonal therapy, according to clinical stage and under international guidance consultation. In this study, pathological confirmation for the suspicious nodes was not performed.

Study background and aims

The present study wants to identify if there are links between background, levels of education, T and N stages in terms of the risk of metastasis or death. Data regarding clinical examination with local evaluation and imaging examination were collected at baseline and reviewed at each subsequent visit. Follow-up visits were scheduled every 3 months and all patients were followed up until the event (death or metastasis) or for a maximum of 36 months

After the cancer confirmation, the patients received chemotherapy or hormonal therapy, according to clinical stage and under international guidance consultation. The evolution and response were assessed with clinical examination and CT (chest, abdomen and pelvis) scan every 12 weeks for the first 12 months, then every 24 weeks for the second year and then annually. The disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was requested to objectify progressive disease.

Statistical analysis and study end points

For the statistical analysis, we had two principal end points: OS and PFS considering levels of education,

background and the tumor and nodal status at the time of diagnosis. OS was measured from the date of surgery or biopsy to the date of death or up to 36 months. PFS was measured from the date of surgery or biopsy until the first local or distant recurrence.

For statistical analysis, we used the R program, version 4.0.2. and survminer package. The sensitivity level was 95%, with $p < 0.05$, considered statistically significant. We calculated RMST from baseline up to 36 months (end of study follow- up) considering each risk factor. RMST difference is interpreted as the number of event-free days gained or lost in the 36 months due to breast cancer disease. Due to this short follow-up period, 36 months, the median survival rate could not be calculated [32,33].

Results

The mean age of the patients was 52 (range 27-78, SD=12).

Levels of education

a) Overall survival

In order to determine if the levels of education could play a role in prolonging OS, the group was divided into three subgroups (Figure 1). The first one consisted of the patients who graduated primary school ($n=9$), in the second the patients also graduated from high school ($n=55$) and the last was made up with patients who also graduated from university ($n=79$). In our group of patients (Table I), the RMST and the event percentage were favorably influenced in patients with higher education (long-rank test: $\chi^2 = 11.30$, degrees of freedom = 2, $p = 0.0036$). The event (death) was present in 33.33% of patients with general school, in 10.90% of patients with high school and in 7.59% of patients with graduated university. The RMST OS for patients with general school was 26.70 months, for high school was 34.90 months, compared with patients with university, 35.30 months.

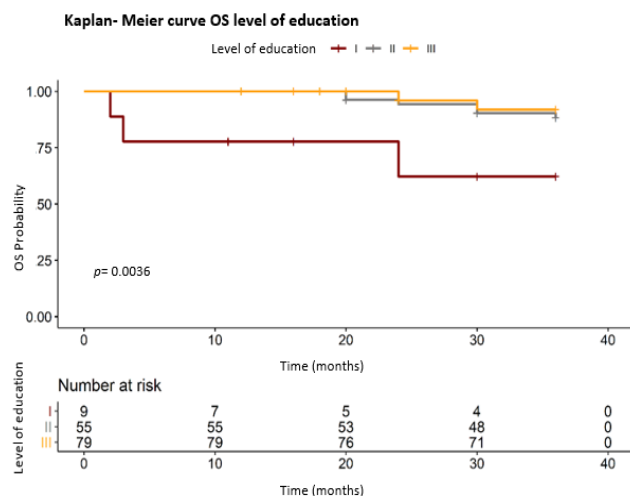


Figure 1. OS levels of education. OS: overall survival. I: general school, II: high school III: university.

Table I. Levels of education survival data.

Level	Events (%)	RMST OS	Median Survival OS [CI95%]
General school	33.33	26.70	N/A
High school	10.90	34.90	N/A
University	7.59	35.30	N/A

N/A: not applicable, RMST: restricted mean survival time. CI: confidence interval.

In order to estimate the death hazard ratio (HR), we calculated the independent predictors for this event. In our group of patients (Table II), graduation of general school only is associated with an increased risk of death, 10.2 times more than for patients with a university degree, with a confidence interval (CI) 2.38 to 43.57 (Table II).

Table II. HR prediction levels of education.

Predictor	Coefficient	p value	HR [CI95%]
Studies	Reference	-	-
General school	2.32	0.0017	10.20 [2.38 la 43.57]
University	0.73	0.2128	2.08 [0.65 la 6.63]

HR: hazard ratio.

b) Progression free survival

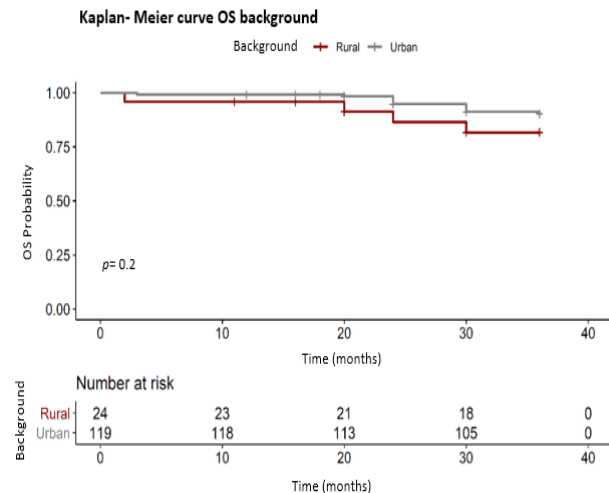
Regarding the PFS, levels of education did not have a statically significant impact (long- rank test: $\chi^2 = 5.10$, degrees of freedom = 2, p value=0.0080). The PFS RMST was 24.40 months for general school, 30.70 for high school and 33.20 for university.

Background

a) Overall survival

Most of the patients (83%, n=119) included in our study came from large cities in Romania, namely from the urban background (Figure 2). The RMST for the patients from the urban background was 34.90, while for the women who came from the rural areas the RMST was 33.00 (Table

III). Although the OS is longer for the people with an urban background, no statistically significant differences were observed (long- rank test: χ^2 was 1.6, degrees of freedom = 1 and the p value=0.2000).

**Figure 2.** OS background.**Table III.** OS survival data.

Strata	Events (%)	RMST OS	Median Survival OS [CI95%]
Rural	16.66	33.00	N/A
Urban	9.24	34.90	N/A

Clinical staging

As illustrated in table IV, we presented the distribution of patients according to the levels of education, background, T and N stage. In this cohort the group of patients came from the urban areas and graduated high levels studies had lower T and N stage tumors.

In this chapter we presented the independently calculated the OS and PFS for T and N stage.

Table IV. Patients and their characteristics.

Characteristics	T1-T2 (%)	T3-T4 (%)	N0-N1 (%)	N3-N4 (%)
Levels of education				
General school (n=9)	3 (33%)	6 (67%)	5 (55%)	4 (45%)
High school (n= 55)	33 (60%)	22 (40%)	38 (69%)	17 (31%)
University (n=79)	51 (64%)	28 (36%)	51 (64%)	28 (36%)
Background				
Rural (n=24)	10 (41%)	14 (59%)	11 (45%)	13 (55%)
Urban (n= 119)	79 (69%)	35 (31%)	86 (72%)	33 (28%)

Tumor stage

a) Overall survival

In our cohort (Figure 3), 37 of patients were classified as T1 tumors (≤ 20 mm in greatest dimension), 53 of patients had T2 tumors (> 20 mm- ≤ 50 mm), 16 of patients had T3 tumors (>50 mm in greatest dimension) and 36 of patients had T4 tumors. Of these, 14 had T4a tumors (extension to the chest wall), 7 of patients had T4b tumors (ulceration), 3 of patients had T4c tumors and 12 had T4d tumors (inflammatory carcinoma). As shown in table V, in our group of patients, there were no statistical differences in OS between the survival curves (the log-rank test: $\chi^2 = 2.70$, degrees of freedom = 3, $p = 0.4500$).

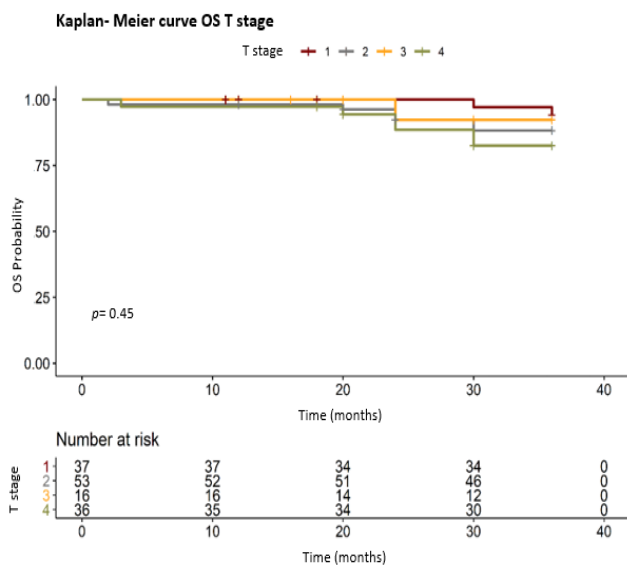


Figure 3. OS T stage. T: tumoral stage.

Table V. Tumoral stage survival data.

Strata	Events (%)	RMST OS	Median Survival OS [CI95%]
Stage T1	5.45	35.80	N/A
Stage T2	11.76	34.30	N/A
Stage T3	6.25	35.10	N/A
Stage T4	16.66	33.60	N/A

b) Progression free survival (PFS)

Regarding the PFS, T stage did not statistically significantly impact this group of patients (long- rank test: χ^2 was 2.00, degrees of freedom= 3, and the p value was 0.5700).

Nodal (N) stage

a) Overall survival (OS)

In this study we considered a lymph node clinically suspicious if it met one of the following criteria: palpability

at physical examination or suspicious imaging features. Suspicious lymph nodes were positive in 65% ($n=93$) of patients, of these 64 % ($n=60$) had N1 stage (movable level I, II axillary lymph nodes), 27% ($n=26$) had N2 stage (fixed or matted level I, II axillary lymph nodes) and 9% ($n=7$) had N3 stage (ipsilateral infraclavicular, ipsilateral internal mammary nodes, ipsilateral supraclavicular, with or without level I, II axillary LN involvement), figure 4. Of those, 3 of patients had imaging involvement in infraclavicular lymph nodes and 4 of patients had positive ipsilateral internal mammary. As shown in table VI, patients with N2 and N3 had a more severe evolution with a higher percentage of events and a low RMST (32.60 months for N3 vs. 35.50 months for N0), long-rank test: $\chi^2 = 7.70$, degrees of freedom = 3, $p = 0.0500$).

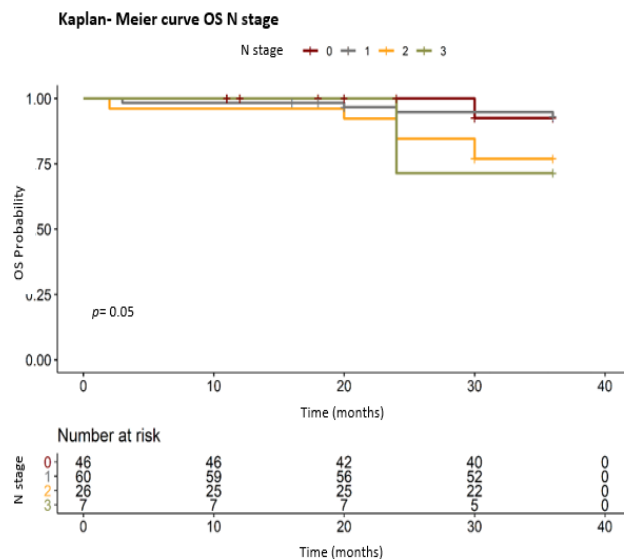


Figure 4. OS N stage. N: nodal stage.

Table VI. Nodal stage survival data.

Strata	Events (%)	RMST OS	Median Survival OS [CI95%]
Clinical N0	6.52	35.50	N/A
Clinical N1	6.66	35.00	N/A
Clinical N2	23.07	32.70	N/A
Clinical N3	28.57	32.60	N/A [24.00 at N/A]

b) Progression free survival (PFS)

Like OS, the clinical or imaging impairment of the lymph nodes was proportional to the decrease of the PFS (Figure 4). Patients with N2 and N3 tumor stages had progressed faster than the other, with a shorter PFS (long-rank test: $\chi^2 = 17.30$, degrees of freedom = 3, $p = 0.0006$). The PFS RMST was 26.80, equal for both N2 and N3 stages (Table VII).

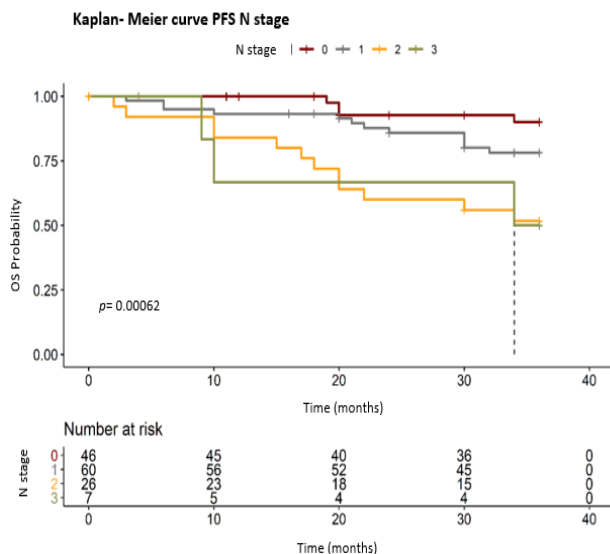


Figure 5. PFS N stage. PFS: progression free survival.

Table VII. Nodal stage survival data.

Strata	Events (%)	RMST OS	Median Survival OS [CI95%]
Stage N0	8.69	34.80	N/A
Stage N1	20.00	32.50	N/A
Stage N2	46.15	26.80	N/A [20.00 at N/A]
Stage N3	42.85	26.80	N/A [10.00 at N/A]

Discussion

Through this study we want to investigate whether background, levels of education and clinical stage of the tumor and lymph nodes may influence the survival of a patient cohort treated for early BC. This study was carried out over a period of 6 years in a University hospital in Bucharest, Romania and included 143 patients.

RMST analysis is a useful approach that can improve clinical interpretability of HRs by placing the results on a time scale that can be understood intuitively. In addition to interpretability, RMST analysis has methodological advantages over HRs. In Cox proportional hazards models, which are widely used to estimate HRs, a core assumption is that the ratio of the hazard rate in the treatment group to that in the control group is constant throughout study follow-up (proportional hazards assumption). Violation of this assumption is common. Evidence of nonproportionality was observed in 24% of 54 cancer clinical trials [31,33-36].

The present study has some potential limitations. The median follow-up time of 36 months is relatively short for BC patients, since late metastasis is common in late evolution. Despite the six years' time frame of this study, only 143 women fulfilled the selection criteria for the current study. Each patient that took part in the study was approved to be treated by a multidisciplinary team and received the

treatment according to the stage of the disease and the tumor subtype. All therapies were given under international guidance consultation. In addition, we had some patients with delayed scheduled treatment, i.e. with less dose intensity, and also some patients with adverse events (anemia, febrile neutropenia, hypersensitivity reactions) for whom it was necessary to postpone the treatment, to adjunct chemotherapy treatment or to interrupt it.

Other potential limit to be considered is that it is a retrospective study that included a low proportion of population from the rural area. However, through the obtained results we consider that it can draw attention to the lack of breast cancer screening and poor access to medical services of the rural residents and the ones with a low level of education.

The background, the levels of education and census-tract- level poverty are well- documented disparities which may negatively influence the BC disease through the contribution brought directly in the prevention, but also in the treatment of this malignance [37-39].

The primary focus of this study was to correlate the impact of the levels of education and the background on OS and PFS. In our group of patients, 55% of patients graduated from a university. Their OS was longer than that of the other patients, with RMST= 35.30 months statistically significant (p -value=0.0036). More, it is observed that levels of education have influenced the death HR, the patients who finished only 8 school classes had an independent risk of death 10.2 times more than patients with university. Regarding the PFS, levels of education did not have a statically significant impact.

Despite the numerous published papers that have specifically examined the relationship between background and cancer survival, questions persist because of inconsistent conclusions. Possible explanations for this inconsistency include differences in the research question being asked (e.g., impact of socioeconomic status on survival in the general population or impact in a clinical trial population), the patient population (e.g., homogeneous or heterogeneous histology or stage, as well as the national, racial, and ethnic composition), sample size or power considerations, the data source (e.g. hospital units or cancer institutes), and the last but not the least how socioeconomic status was quantified [40,41].

Most of the patients (83%, $n=119$) included in our study came from large cities in Romania, so from an urban background. Although both the RMST OS and PFS were longer for women coming from the urban background, the correlation was not statistically significant. This aspect may be due to the fact that in this group of patients were predominantly included patients from urban areas, given that the hospital is in the first category, in the center of the capital. The survival impact of those patients is probably due to the presentation in advanced stages of disease.

In a Nurses' Health Study of women with breast cancer, Kroenke et al. found that socially isolated women were twice as likely to die from breast cancer than socially integrated women [42].

All patients included in this study, after raising the suspicion of BC, clinical or imaging, were evaluated in the multidisciplinary board. Considering the stage at the moment of diagnosis, the patients were referred to the medical oncology for the initiation of the neoadjuvant chemotherapy or to surgery. For all the patients included in this study, the clinical assessment of the T and N stage was performed before any oncological treatment.

Tumor size has been recognized for years as a factor with prognostic importance for breast cancer. More recently, the prognosis and the planning for delivering neoadjuvant therapy have been based on lymph node, menopausal status, estrogen, progesterone receptor and Her 2/neu status. In our study, clinical tumor size measurement does not impact the outcome, but further longer studies are necessary [43].

Up to the 1990s, the surgical treatment of invasive breast cancer included axillary lymph-node dissection. Axillary dissection served both as a regional staging procedure and as a treatment. However, the short-term and long-term side-effects of axillary dissection were always of concern. Although the axillary dissection is a debatable procedure in the early-stage BC, in this study we evaluate clinically the lymph nodes, before receiving any oncologic treatment. In our group of patients, the presence of N2, N3 disease impact both the OS (p -value =0.05) and PFS (p -value=0.0006), with low RMST for the advance involvement [40].

RMST provides an intuitive, explicit way to express the effect BC patients have on OS and PFS after the primary treatment according to clinical stage and under international guidance consultation. RMST allows a more personalized interpretation of the benefits and risks of other risk factors which may negatively influence the survival. Because RMST is intuitively interpreted and conveniently estimated using standard statistical software, we recommend that it be routinely reported in conjunction with HRs and absolute rates in clinical studies evaluating medical interventions. Future research is warranted to investigate how RMST can improve communication between clinicians and patients and influence treatment choices [44,45].

Conclusions

In conclusion, RMST provides an intuitive and explicit way to express the effect of background, levels of education, T and N stage on a BC group of patients in terms of PFS and OS. This measure allows a more personalized interpretation than HR on the benefits and risks of a medical intervention for decision-making.

Low level of education and high-grade clinical lymph node status negatively influences the outcome of this cohort of BC patients. Our study has not shown that clinical

tumor stage may confer a worse prognosis, but additional studies could also better define the clinicopathological characteristics associated with clinical tumor characteristics and help determine the role of palpability as a prognostic indicator.

Background did not impact OS or PFS, but a larger proportion came from urban areas, so further research is required to demonstrate the effects. This aspect is important to intensify the prevention measures especially in rural areas.

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