RESEARCH ARTICLE

Multivariate Analysis of Prognostic Factors in Male Breast Cancer in Serbia

Sandra Branko Sipetic-Grujicic[1]*, Zafir Hajdar Murtezani[2], Zora Borivoje Neskovic-Konstatinovic[3], Jelena Milutin Marinkovic[4], Vladimir Nikola Kovcin[2], Zoran Gojko Andric[2], Sanja Vladeta Kostic[2], Isidora Stojan Ratkov[1], Jadranka Milutin Maksimovic[1]

Abstract

Background: The aim of this study was to analyze the demographic and clinical characteristics of male breast cancer patients in Serbia, and furthermore to determine overall survival and predictive factors for prognosis. Materials and Methods: In the period of 1996-2006 histopathological diagnosis of breast cancer was made in 84 males at the Institute for Oncology and Radiology of Serbia. For statistical analyses the Kaplan-Meier method, long-rank test and Cox proportional hazards regression model were used. Results: The mean age at diagnosis with breast cancer was 64.3±10.5 years with a range from 35-84 years. Nearly 80% of the tumors showed ductal histology. About 44% had early tumor stages (I and II) whereas 46.4% and 9.5% of the male exhibitied stages III and IV, respectively. Only 7.1% of male patients were grade one. One-fifth of all patients had tumors measuring ≤2 cm, and 14.3% larger than 5 cm. Lymph node metastasis was recorded in 40.4% patients and 47% relapse. Estrogen and progesterone receptor expression was positive in 66.7% and 58.3%, respectively. Among 14.3% of individuals tumor was HER2 positive. About two-thirds of all male patients had radical mastectomy (66.7%). Adjuvant hormonal (tamoxifene), systematic chemotherapy (CMF or FAC) and adjuvant radiotherapy were given to 59.5%, 35.7% and 29.8% patients respectively. Overall survival rates at five and ten years for male breast cancer were 55.0% and 43.9%, respectively. According to the multivariate Cox regression predictive model, a lower initial disease stage, a lower tumor grade, application of adjuvant hormone therapy and no relapse occurrence were significant independent predictors for good overall survival. Conclusions: Results of the treatment would be better if disease is discovered earlier and therefore health education and screening are an imperative in solving this problem.

Keywords: Breast cancer - men - survival analysis - predictors

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Introduction

The etiology of breast cancer in male has been hardly studied, because the disease is very rare (Weiss et al., 2005; Contractor et al., 2008; Schaub et al., 2008). However the incidence of breast cancer in male's population is on the constant increase (Weiss et al., 2005). Distribution of male breast cancer is higher in North America and West Europe, while lower in Asia and Africa (for almost 15%) (Ravandi-Kashani and Hayes, 1988).

Due to ignorance, the disease is often discovered late in men, which is associated with more advanced disease (higher stage of disease, larger tumors and more lymph node positive disease) (Nahleh et al., 2008). In Brazilian study in which 75 male breast cancer patients was included, independent factors associated with increased risk of death were metastasis at diagnosis, older age (≥65 years), higher tumor stage (≥IIb) and positive smoking status (Bergmann et al., 2012). But in study conducted in United States among 2,475 men, age (above 65 years), size and grade of a tumor, involvement of lymph glands and steroid receptors status were identified as independent prognostic factors for breast cancer survival in male (Talluri et al., 2011).

Treatment of breast cancer in male most often includes radical mastectomy, possible postoperative radiotherapy, chemotherapy and/or hormone therapy on the basis of consensual guides for female breast cancer treatment (Lanitis et al., 2008). A better understanding of this disease is needed so that new opportunities for early detection and therapeutic intervention may be developed.

The aim of this study was to analyze the demographic and clinical characteristics of male breast cancer patients in Serbia, and furthermore to determine overall survival

*[1]Institute of Epidemiology, [4]Institute of Medical Statistics and Informatics, Faculty of Medicine, Belgrade University, [2]Clinical Hospital Centre Bezanijska Kosa, [3]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia *For correspondence: sandra.grujicic@mfub.bg.ac.rs, ssipetic@yahoo.com*

and predictive factors for prognosis of this cancer.

Materials and Methods

In the period from 1st January 1996 till 31st December 2006 histopathological diagnosis of breast cancer was set in 84 male at The Institute for Oncology and Radiology of Serbia. We only included patients with a single primary breast cancer. Patients with a second primary breast cancer, two or more primary breast cancers, or a primary tumor in another organ were excluded from the study. Patients and tumor characteristics were obtained from medical records.

Demographic information included age at diagnosis (≤65, >65), place of living (urban/rural), occupation (farmer or industrial worker/other - jurists, doctors, teachers, economists) and education (elementary or secondary school/university). From all patients family history for cancer diseases was used. Tumor characteristics were classified by stage (I, II, III, IV), grade (1, 2, 3, 4), estrogen receptor (ER) and progesteron receptor (PR) status (positive, negative, unknown), human epidermal growth factor receptor-2 (HER-2) status (positive, negative, unknown), size (≤2cm/2-5cm, >5cm), nodal involvement (0/1-3/4/7/8+) and type of tumor (invasive ductal cancer/ invasive lobular cancer/ other - mixed, Paget). HER-2 status was determined using a combination of the fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Values of 2.3 or higher for FISH and values of 3+ for IHC were classified as positive. The absence of distant metastases was estimated by clinical check-up and additional diagnostic procedures: RTG of the lungs, scintigraphy of the skeleton, X-ray check-ups, CT or NMR check-ups. Disease stage, nodal involvement and the presence of metastases were determined on the basis of TNM classification (American Joint Committee on Cancer, 2010).

Treatment characteristics included surgery (none/ partial mastectomy - lumpectomy/total mastectomy), adjuvant chemotherapy, adjuvant radiotherapy and adjuvant hormonal therapy (Giordano et al., 2005). Patients who did not receive any formal resection of their primary tumor or who only underwent breast biopsies for tissue diagnosis were categorized as not having surgery. Patients were, on the basis of prognosis factors, treated with adjuvant chemotherapy and/or radiotherapy and/or hormonal therapy Nolvadex, according to The National Guide. From chemotherapy they received CMF (-Ciklofosfamid, Metotreksat, 5-Fluorouracil) or FAC protocol (-5-Fluorouracil Doxorubicin, Ciklofosfamid). In the metastatic stage cases were treated by mixed therapy (hormonal and/or chemotherapy and/or radiotherapy). The outcome was determined by assessing the patient's current status (alive or dead) at the time of last contact. The exact data on the causes of death were not available to us.

The study was approved by The Ethical Committee of The Faculty of Medicine, University of Belgrade.

Survival analysis was performed using the Kaplan-Meier method and long-rank test for group comparison of survival curves. Survival was defined as the period from moment of breast cancer diagnised (as zero time) till death or last contact (as the end point). Univariate and multivariate analysis based on the Cox regression model were conducted to identify prognostic factors associated with progression overall survival. A backward stepwise procedure was used. For all calculations, SPSS software was used. A p value of less than 0.05 was considered to be statistically significant.

Results

The 84 male breast cancer patients were included in study. On January 31th, 2012, 37 (44.0%) patients were still alive and 45 (53.6%) patients were dead and for two (2.3%) patients status was unknown. The mean age at diagnosis of male breast cancer was 64.3±10.5 years with age ranging from 35-84 years. The mean of overall survival from breast cancer onset was 72.8±42.1 months with the follow up period ranging from one till 216 months. The demographic characteristics for 84 male breast cancer patients are shown in Table 1. Among men with breast cancer were more people aged ≤65 years (53.6%) and with lower education (89.2%). Approximately two thirds of the patients were from urban arrears in Serbia. The most of them were farmers or industrial workers (88.9%). Positive family history of cancer was present in 29.8% patients and among them only 14 (16.7%) had relatives with breast cancer.

Nearly 80% of the tumors in men showed ductal and 14.3% lobular histology (Table 1). About 44% of the male patients had early tumor stages (I and II) whereas 46.4% and 9.5% of the male showed tumor stage III and IV respectively. Only 7.1% of male patients were grade 1. One-fifth of all patients (20.2%) had tumors measuring <2cm, and 14.3% had tumor >5 cm in total dimension. Male patients with lymph node metastasis were found in 40.4% patients but this status was unknown for 35.7% patients. About 50% of male patients had metastasis of which 21.2% in soft tissue, 31.8% in bone and 28.7% in viscera. All others (18.3%) had multiple metastases. Relapse was recorded in 47% of men with breast cancer.

Treatment details for 84 male breast cancer patients are shown in Table 1. Estrogen and progesterone receptor expression was positive in 66.7% and 58.3% respectively. Twelve (14.3%) Tumors were HER2 positive among 14.3% of individuals. About two-third of all male patients had radical mastectomy (66.7%). Adjuvant hormonal (Tamoxifene), and systematic chemorherapy (CMF or FAC) and adjuvant radiotherapy were given to 59.5%, 35.7% and 29.8% patients respectively.

Overall survival rates at one, three, five and ten years for male breast cancer were 89.0%, 71.0%, 55.0% and 43.9%, respectively (Figure 1).

The average survival of men with breast cancer was significantly longer if they had: a lower initial stadium of the disease ($p<0.001$); a lower tumor grade ($p=0.001$); a lower tumor size ($p=0.002$); if they were without positive lymph nodes ($p=0.005$); without positive PR receptors ($p=0.023$); without metastases ($p<0.001$); without relapse of the disease ($p<0.001$); if mastectomy was performed ($p<0.0001$); and if they got adjuvant hormone therapy ($p=0.021$) (Table 2). A significant difference in survival

Table 1. Patients Demographics

Variable	Category	No. (N=84)	%
Patients demographics:			
Age (years)	≤65	45	53.0
	>65	39	46.4
Living place	Urban	57	67.9
	Rural	27	32.1
Education level	Primary/secondary	75	89.2
	University	9	10.8
Occupation	Farmer, industial worker	40	88.9
	Other	5	11.1
Family history of cancer	Yes	25	29.8
	No	59	70.2
Tumor Characteristics:			
Type of tumor	Invasive ductal cancer	66	78.6
	Invasive lobular cancer	12	14.3
	Other*	6	7.1
Initial stage of tumor	I	5	6.0
	II	32	38.1
	III	39	46.4
	IV	8	9.5
Grade	1	6	7.1
	2	63	75.0
	3	15	17.9
Size of tumor (cm)	≤2	17	20.2
	2.1-5	24	28.6
	>5	12	14.3
	Cancer mastitis	11	13.1
	Unknown	20	23.8
No. of positive nodus	0	20	23.8
	1-3	16	19.0
	4-7	10	11.9
	>8	8	9.5
	Unknown	30	35.7
Metastasis	Yes	39	46.4
	No	45	53.6
Localisation of metastases	Soft tissue	8	21.2
	Bone	12	31.8
	Visceral metastases	11	28.7
	Multiple metastases	8	18.3
Relapse	Yes	40	47.0
	No	44	53.0
ER status	Positive	56	66.7
	Negative	25	29.8
	Unknown	3	3.6
PR status	Positive	49	58.3
	Negative	32	38.1
	Unknown	3	3.6
HER2 receptors	Positive	12	14.3
	Negative	71	84.5
	Unknown	1	1.2
Treatment Details of Male Breast Cancer:			
Type of surgery	None	17	20.2
	Lumpectomy	11	13.1
	Radical mastectomy	56	66.7
Adjuvant hormonal therapy (Tamoxifen)	Yes	50	59.5
	No	34	40.5
Adjuvant systemic chemotherapy*	Yes	30	35.7
	No	54	64.3
Adjuvant radiotherapy	Yes	25	29.8
	No	59	70.2

*CMF (Cyclophosphamide+Methotrexate+5-fluorouracil) or FAC protocol (5–fluorouracil+Doxorubicin+Cyclophosphamide)

has not been received in respect of all other variables.

All variables with p value≤0.1 according to the univariate Cox regression model (initial stage of tumor, grade, size of tumor, number of positive lymph nodes, metastasis, ER status, PR status, type of surgery, adjuvant hormonal therapy with Tamoxifen, adjuvant systemic chemotherapy and relapse) were included in the multivariate Cox regression predictive model (Table 3).

Table 2. Five-Year Overall Survival Rates, Mean Survival Time and Log-Rank Test by Variable

Variables	Category	5-year cumulative overall survival (%)	Mean survival of time from onset±SD (month)	p value for Log-rank test
Initial stage of tumor	I	100	216.0±0	
	II	87	124.0±7.8	
	III	38	80.5±11.5	
	IV	0	22.3±6.4	<0.001
Grade	1	100	110.0±13.4	
	2	63	118.8±12.6	
	3	13	43.9±9.8	<0.001
Size of tumor (cm)	≤2	100	138.5±6.8	
	2.1-5	70	97.2±9.7	
	>5	38	94.5±24.5	
	Cancer mastitis	45	73.8±11.1	0.002
Number of positive nodus				
	0	90	129.9±8.8	
	1-3	87	121.1±12.6	
	4-7	40	97.8±24.1	
	>8	63	68.6±7.0	0.005
Metastasis	Yes	35	116.2±7.9	
	No	77	71.0±10.0	<0.001
Localisation of metastases				
	Soft tissue	33	106.3±18.4	
	Bone	50	70.3±15.4	
	Visceral metastases	18	50.4±9.7	
	Multiple metastases	8	28.6±10.0	0.007
PR status	Positive	69	102.3±7.6	
	Negative	38	86.7±14.9	0.023
Type of surgery	None	17	124.0±14.7	
	Lumpectomy	44	66.0±14.3	
	Radical mastectomy	74	50.6±11.3	<0.001
Adjuvant hormonal therapy (Tamoxifen)				
	Yes	71	102.5±7.3	
	No	36	91.0±15.2	0.021
Relapse	Yes	35	116.4±8.3	
	No	77	71.4± 9.4	<0.001

*CMF (Cyclophosphamide+Methotrexate+5-fluorouracil) or FAC protocol (5 –fluorouracil+Doxorubicin+Cyclophosphamide)

Table 3 Univariate and Multivariate Cox Regression Model

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p*	OR (95%CI)	p*
Initial stage of tumor	5.4 (3.2-9.2)	<0.001	5.3 (1.6-17.1)	0.006
Grade	3.3 (1.8-6.2)	<0.001	6.9 (1.7-27.4)	0.006
Size of tumor	1.8 (1.3-2.6)	<0.001		
No of positive lymph nodes				
	1.9 (1.3-2.9)	0.001		
Metastasis	3.8 (2.0-7.2)	<0.001		
Relapse	4.0 (2.0-7.9)	<0.001	4.2 (1.03-17.3)	0.044
PR status	0.5 (0.3-0.9)	0.027		
Type of surgery	0.5 (0.4-0.7)	<0.001		
Adjuvant hormonal therapy				
	0.5 (0.23-0.9)	0.024	6.2 (1.1-34.8)	0.039

*CI-confidence interval, OR-odds ratio, PR-progesterone

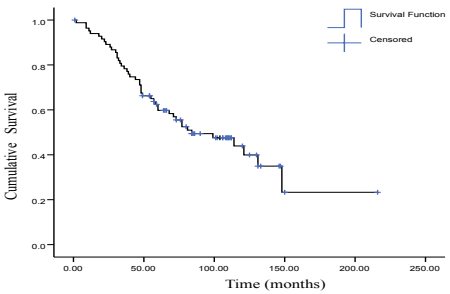

Figure 1. Kaplan-Meier Curve for Overall Cumulative Survival of Male with Breast Cancer

According to the multivariate Cox regression predictive model, a lower initial disease stage, a lower tumor grade, application of adjuvant hormone therapy and no relaps occurrence were significant independent predictors for improving overall survival in male breast cancer.

Discussion

In this study, 5- and 10-years of overall survival for breast cancer in men were very low and amounts 55.0% and 43.9%, respectively. But in the Germany study conducted on 67 men and 67 women 5-years of overall survival were 71.4% and 70.3% in men and women, respectively (Foerster et al., 2011). The reason for such low survival rate in our country is in the fact that the diagnosis of this disease is set late and that at the moment of diagnosis in men advanced stage of the disease already exists (55.9% of patients had III or IV stage of the disease). In contrast to women who confide to a few people as soon as they notice the first symptoms of breast cancer (Volkers, 1999), men delay to visit their doctor for 6-8 months from the appearance of symptoms (Goss et al., 1999). This tells us about bad social and health habits of men which are present in our country as well. No recommendations for self-examination or examination of the male breast by physicians exist. Also no guidelines recommend screening mammography at any age for men because this disease is very rare. Relative risk of a second breast cancer appearance in a treated man is 30 times higher than in women, which shows that health awareness of this disease is necessary, especially in men's population (Auvien et al., 2002; Gomes-Raposo et al, 2010). Also, interventions are needed that effectively and efficiently target the personal motivation of at risk men to seek out and engage in breast cancer prevention, similarly as it is with Asian women (Ahmadian and Abu Samah, 2013).

In our research average age of male with breast cancer was 64.3±10.5 years. It is noticed in many studies that breast cancer most often appears between 60 and 70 years of age in male (Talluri et al., 2011). Male breast carcinoma in the veteran population is a disease of older men and presents approximately 10 years later than does female breast cancer (De Perrot et al., 2000). Older age at diagnosis is associated with higher frequency of comorbidities, which likely explains the overall poorer survival among men. In the studies in which the groups of males and females were similar according to age and disease stage there was no difference in the overall survival rates (Giordano et al., 2004; Gomes-Raposo et al., 2010).

Giordano et al. (2004) showed that five year rate of overall survival for breast cancer in men was 78% in T1 stage, 67% in T2 stage, 40% in T3 stage and 19% in T4 stage. Five year survival for patients without involvement of lymph glands was 70%, whereas in patients with dissemination of the disease into lymph glands 37-54% (Yildirim and Berberoğlu, 1988). In our study five year survival of men with breast cancer in relation to stage of the disease is much lower and amounts to 100% for T1 stage of the disease, T2 stage 87%, T3 stage 38%, while for T4 stage 0%. In numerous studies the clinical stage of disease is identified as a significant independent prognostic factor for survival of men with breast cancer (Vaizey et al., 1999), and even as a separate risk factor independent from tumor size or lymph node metastasis (Contractor et al., 2008; Schaub et al., 2008; Gomes-Raposo et al., 2010). In our study, a lower initial disease stage, a lower tumor grade, application of adjuvant hormone therapy and no relaps occurrence were independent predictors of a favorable outcome of breast cancer in males.

Tumor size and lymph glands involvement represent two obvious prognostic factors for breast cancer in men if it is not disseminated (Salvadori et al., 1994; Schaub et al., 2008). Men with tumor size from two to five cm have for 40% greater risk of death in comparison to men who have a tumor smaller than 2cm (Mustafa et al., 1998), that is five year survival of men with breast cancer smaller than 2cm is 74%, while 37% in those with a tumor greater than 5cm (Guinee et al., 1993). In our study the rate of overall five year survival of men with breast cancer in relation to tumor size is 100% for tumors ≤2cm, and 38% for tumors greater than 5cm.

Similarly, patients with lymph nodes involvement have for 50% greater risk of death than those without lymph nodes involvement (Heller et al., 1998). A greater number of positive nodes is also associated with a worse prognosis (Joshi et al., 1996). One of the studies showed that the status of axillary lymph nodes was the only statistically significant independent prognostic factor (Berg and Hutter, 1995). In our study men with breast cancer who do not have positive lymph nodes have a longer five year survival (90%) in comparison to persons with one or more positive nodes (from 87% till 35%).

Two most common pathohistological types are ductal invasive carcinoma (93.7%) and lobular carcinoma (1.8%) (Bruce et al., 1996), which is also shown in the results of our research (ductal invasive carcinoma-78.6% and invasive lobular carcinoma - 14.3%).

Etiology of breast cancer in male is still unknown because the disease is very rare, and on the other side the size of a tumor is in most cases very small. In our study the size of breast tumor was less than 5cm in about two thirds of male with breast cancer. Therefore, after the necessary pathohistological analysis there is no sufficient tissue left for molecular and genetic researches. Risk factors for breast cancer development in male include positive family history for breast cancer, exposure to radiation and high temperatures, excessive alcohol consumption and states in which the level of hormone estrogen increases (Klinefelter's syndrome, gynecomastia and other) (Sasco et al., 1993; D'Avanzo and La Vecchia, 1995). In our study about 30% of male with breast cancer had positive family history for some cancer. It is well known that carriers of BRCA1 and BRCA2 mutations are predisposed to high lifetime risk of breast cancer (Mahdi et al., 2013). Mutation in BRCA1 and BRCA2 gene in females also increased the risk of pancreatic cancer and other cancers, while in males it increased the risk of prostate cancer, pancreas cancer and breast cancer (Thompson et al., 2005).

Treatment of breast cancer most often involves radical mastectomy, possible postoperative radiotherapy, chemotherapy and/or hormone therapy based on consensual guides for the female breast cancer treatment.

In our research radical mastectomy was surgery choice in 2/3 of men, which corresponds with literature data (Yildirim and Berberoğlu, 1998). However, the same, most often applied St Gallen consensus can not be absolutely applied to men due to sex difference that significantly influences therapy choice, although male breast cancer behaves similarly as postmenopausal breast cancer in women (Early Breast Cancer Trialist Collaborative group, 2005; Goldhirsch et al., 2011). Majority of men is treated with modified radical mastectomy by axillary dissection or sentinel node biopsy. Radical mastectomy is often carried out, but retrospective studies showed that results are almost the same as in those who had less invasive operation (Cimmino et al., 2004). Sparing operations are applied as well, but in a lesser scope and at patient's request. Numerous studies showed that sentinel node biopsy had a little specificity and sensitivity, and therefore it is not recommended (Cimmino et al., 2004).

Contemporary understanding of the appearance of subclinical micro metastases during the time of surgical procedure explains the necessity of applying additional "adjuvant" systemic treatment for the greatest number of patients that is proved to prolong survival. Adjuvant therapy is applied after the operative procedure in the form of chemotherapy and/or hormone therapy. Adjuvant therapy is a choice therapy in patients with present metastases. In our research there were about 50% of men with present metastases at the moment of setting the diagnosis, with no difference regarding the localization. Adjuvant chemotherapy was applied in around 36% of men.

Breast carcinoma in men, similarly as in women, can be hormone sensitive and hormone resistant, and therefore it is compulsory to determine the status of steroid tumor receptors (estrogen receptors - ER and progesterone receptors - PR) and do HER-2 analysis. On average 90% of all male breast cancers have ER expression, while 76% have PR expression (Bruce et al., 1996). Negative hormone status is associated with bad prognosis (Fentiman et al., 2006). In our study 66.7% of men had ER expression and 58.3% had PR expression. HER-2 expression was present in 14.3% of men, which is similar to the frequency of appearance in other studies (15% of the sick) (Slamon et al., 1987; Roset al., 2003; Agrawal et al., 2007; Wolff et al., 2007). It points out to bad prognosis. In retrospective Turkey study estrogen and progesterone receptor status was independently associated with overall survival (Olmez et al., 2013), but in our study it was not case.

Since the majority of breast cancers are hormone dependant in its growth, with that in mind it is responsive to hormone manipulations. Standard of hormone therapy in the first line is antiestrogene Tamoxifen (Ribeiro and Swindell, 1992). Clinical investigations show that the benefit of Tamoxifen therapy can also be achieved with the receptor negative tumors, but to a lesser extent, and that most possibly originates from the response of those patients whose receptors are negative, but present. Therefore, difference must always be made between the patients who are completely without receptors and those with low level receptors. Standard of adjuvant hormone therapy with Tamoxifen was used in 59.5% of our patients. In the foreseeable future, drug treatment may be guided by individualized genotype databases that can enable customized drug dosing to minimize toxicity and to enhance therapeutic effect (Xu et al., 2013).

To our knowledge, this is the first study to evaluate male breast cancer in Serbian population with long-term survival data. Limitations include the retrospective design of the study; the inclusion of many patients with unknown nodes status and size of tumor; and an absence of detailed treatment records. In addition, data on specific causes of death were not available.

In conclusion, breast cancer in men in Serbia is more often discovered in higher clinical stages, as well as in other developing countries. Five and ten year of overall survival would be much better if the disease was discovered in earlier stages. It is obvious that there is a lack of community-based and qualitative studies regarding breast cancer prevention among men in Serbia. It is important to increase awareness of male breast cancer so that it is diagnosed earlier (general information about disease, health promoting TV ads, a telephone help-line for male cancer, posters about breast cancer in pubs, shops or in places where men go, etc.). Education, an appropriate system for early detection (screening), and adequate treatment are necessary for improving survival. A better understanding of this disease is needed so that new opportunities for therapeutic intervention may be developed.

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