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ORIGINAL ARTICLE

Clinical and biological characteristics of breast cancer

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Summary

Purpose: *In view of the crucial importance of early detection and diagnosis of breast cancer for subsequent treatment and prognosis, the aim of this study was to identify clinical and biological characteristics of breast cancer at the time of diagnosis.*

Methods: *The study enrolled 449 breast cancer patients in Clinical Centre Nis. Results were analyzed using Student's t-test for paired and unpaired samples, chi-square test, Mantel-Haenszel test and Fisher's test of exact probability.*

Results: *The average patient age was 56.2±12 years (range 23-85). Seventy-three percent of the affected women were postmenopausal and 8.3% below 40 years of age. Operable disease was identified in 78% of the cases, and metastatic in 3.6%. TNM clinical stage IIA was identified in 27.6% of the patients, T2 in 49.2% and Tis in 0.9%. Almost 44% had negative axillary lymph nodes. Most common monolocalization of metastatic disease was the liver and the supraclavicular lymph nodes, and combined localization was the liver and bones. Histologic and nuclear grades 2 and ductal carcinoma were most common. Estrogen receptor positive (ER+) status was 3-fold higher than ER negative (ER-) status. Human epidermal growth factor receptor 2 (HER2) positive patients were most commonly ER-. The most common primary tumor site was the upper lateral quadrant. Left breast was more commonly involved. Radical surgery was the most common type of operation.*

Conclusion: *In view of the unfavorable age of patients at the time of diagnosis and clinical and biological tumor characteristics, the results confirmed that it is of vital importance to provide breast cancer prevention, screening, and to organize breast cancer units according EUSOMA guidelines.*

Key words: biological characteristics, breast carcinoma, clinical characteristics

Introduction

Early detection and diagnosis of breast changes are of utmost importance for further adequate management of possible disease and for survival improvement and mortality reduction of breast cancer patients [1].

Standard prognostic factors used for primary breast carcinoma can be patient-related (age, menopausal status) and tumor-related (size, histologic type, axillary nodal status, histologic and nuclear grade, ER and progesterone receptor (PR) status, proliferative activity).

Bearing in mind the crucial importance of early detection and diagnosis of breast cancer for subsequent treatment and prognosis, survival, and quality of life of the affected women, the aim of this study was to identify clinical and biological characteristics of breast cancer at the time of diagnosis.

Methods

The study enrolled 449 breast cancer patients surgically treated at the Surgical Clinic Nis from January 2003 to December 2005. Patients were put on adjuvant treatment (chemotherapy, hormonotherapy, trastuzumab) based on tumor biological characteristics, at the Clinic of Oncology, Clinical Center Nis, while those with metastatic disease received anticancer treatment (chemotherapy, hormonotherapy, trastuzumab, radiotherapy) based also on tumor biological characteristics and tumor spread, at the same Center. All patients had histopathologic assess-

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ment and diagnosis confirmation at the Institute of Pathology Nis. The data were obtained by way of analysis of medical documentation of the Surgical Clinic and Institute of Pathology, as well as the hospital registry and patient medical records at the Clinic of Oncology.

Patients were stratified according to their age at the time of diagnosis and place of residence.

All of the cases were assessed in regard to the clinical tumor stage, defined as operable, locally advanced, or metastatic disease. They were also analyzed according to their menstrual status (pre and postmenopausal).

With regard to the type of surgery, patients were divided into 3 groups: those with radical surgery, conservative (breast-conserving) surgery, and biopsy.

Biological characteristics of the tumors were determined by way of the analysis of histopathologic data (histopathologic tumor type, histological grade and nuclear grade).

All of the patients for whom receptor status was determined (n=440) were divided into 4 groups, depending on the status of ER and PR. Data analysis was performed related to hormonal sensitivity; patients were thus divided into two subgroups: with hormone sensitive and insensitive disease. At the same time, two patient subgroups were analyzed: HER2 positive and HER2 negative. ER, PR, and HER2 status were determined immunohistochemically. In cases of HER2++, CISH methodology was utilized. Based on positivity, the following patient groups were identified: those with + (+1) moderate, ++ (2+) intermediate, and +++ (3+) strong overexpression and/or amplification of HER2. Patients without overexpression and/or amplification were regarded as HER2 negative.

Statistical considerations

The data were processed using standard descriptive statistical parameters (mean value, standard deviation, percentages). Several tests were applied in the study: Student's t-test for paired and unpaired samples, chi-square test, Mantel-Haenszel test and Fisher's test of exact probability.

Statistical processing was accomplished in Excel 7.0 and SPSS 11.0 in the Windows 98 environment.

Results

The peak incidence was at the 51-60 years age group (29.8%; Table 1). In total, there were 8.3% patients below 40 years of age, ranging from 23 to 40 years (X±SD=35.9±4.3).

Operable disease was registered in 78.2% of the cases, locally advanced in 18.3%, and metastatic disease in 3.6% (Table 2). Those with locally advanced disease were significantly older compared to the other two groups ($p<0.01$; Table 2).

Local and locally advanced disease were most commonly registered in those aged 51-60 years. Locally advanced disease showed an increasing trend with advancing age, while metastatic disease incidence was relatively constant among the age groups.

The average patient age within tumor groups is shown in Table 2.

Related to the place of residence, no differences in incidence for metastatic (3.2 vs. 4.0%) and locally advanced disease (15.5 vs. 22.8%) were observed. There was a statistically significant difference for operable vs. locally advanced cancer: operable disease was more commonly diagnosed in urban dwellers (81.3%) ($x^2=3.84$; $p<0.05$; Table 2).

Postmenopausal women were generally more commonly affected (73.1%) and were 61.2±9.3 years old. Premenopausal women were 43.5±6.5 years on average.

Table 1. Age distribution of breast cancer patients

Age distribution (years)	*<40*	*41-50*	*51-60*	*61-70*	*>70*	*Total*
Number of patients	37	109	134	107	62	449
%	8.2	24.3	29.8	23.8	13.8	100.0

Table 2. Tumor and patient characteristics

Tumor characteristics	*Patients*		*Age (years)*	*Place of residence*	
	Number	*%*	*±SD*	*Urban*	*Rural*
Operable	351	78.2	55.5±11.5*	226**	125
Locally advanced	82	18.3	61.5±11.7	43	39
Metastatic	16	3.6	53.8±11.5*	9	7
Total	449	100.0	56.2±12	278	171

*p<0.01 vs. locally advanced; **p<0.05 vs. locally advanced, SD: standard deviation

Most of the patients had TNM clinical stages IIA (27.6%) and I (18.9%); the lowest percentages were in clinical stage IV (3.6%) and 0 (0.9%) (Table 3).

In women with operable breast cancer, most common was clinical stage IIA (35.4%), then I (24.2%), II-IA (20.5%), while IIB was present in 18.8% and stage 0 in 1.1%.

Most patients (49.3%) had T2 stage tumors. Less commonly identified were Tis (0.9%) and T3 (6.2%) disease stages (Table 4).

In patients with operable clinical stage IIA, stage T2 was the most common finding (41.6%), with slightly unfavorable relationship of T2/T1 in IIA stage group (74.2 vs. 25.8%).

There were 20 (4.5%) patients with tumors in situ and metastatic disease.

In 429 women pN status was determined. An unknown number of involved lymph nodes was registered in 11.6% patients, and 43.6% were without lymph node involvement (Table 5). Patients most commonly (20.1%) had 1-3 positive nodes.

Positive lymph nodes were significantly more common in patients with locally advanced disease (85.9%) compared to those with operable disease (45.9%; $p<0.001$).

In patients with operable disease pN stages were almost evenly distributed, i.e. the numbers of patients with pN1 and pN2 stages were approximately the same. In the group with locally advanced disease, 10 or more nodes were involved in over 60% of the cases, with the relationship of pN1/pN2 being approximately the same as in women with operable disease (Mantel-Haenszel=0.1; $p>0.05$).

The characteristics of metastatic disease at the first visit were studied in 16 (3.6%) patients. Most common monolocalization of metastatic disease was the liver (18.7%), followed by supraclavicular lymph nodes (12.5%), bones (12.5), lungs (6.2%), and malig-

Table 3. TNM clinical stages

	0	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total*
Number of patients	4	85	124	66	72	56	26	16	449
%	0.9	18.9	27.6	14.7	16.0	12.5	5.8	3.6	100.0

Table 4. Pathological T stage in relation to clinical stages

pT stage	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total*
	Number of patients								*n (%)*
Tis	4	0	0	0	0	0	0	0	4 (0.9)
T_1	0	85	32	0	16	0	1	1	133 (29.6)
T_2	0	0	92	57	46	0	21	2	221 (49.2)
T_3	0	0	0	9	10	0	2	8	28 (6.2)
T_4	0	0	0	0	0	56	2	5	63 (14)
Total	4	85	124	66	72	56	26	16	449 (100)

Table 5. Pathological N stage in relation to clinical stages

pN stage	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*Total*
	Number of patients						*n (%)*
pN0	80	88	13	0	6	0	187 (43.6)
pN1	2	26	45	5	8	0	86 (20.1)
pN2	0	2	6	65	5	1	78 (18.2)
pN3	0	0	0	0	0	24	25 (5.8)
pN1(sn)*	1	2	0	0	0	0	3 (0.7)
Unknown	2	6	2	2	37	1	50 (11.6)
Total	85	124	66	72	56	26	429 (100)

*Sentinel lymph node

nant effusions (6.2%). Most common combined localizations were the liver and bones (18.7%), liver, lungs and bones (12.5%), liver and lungs (6.2%), liver and supraclavicular lymph nodes (6.2%).

Most women (81.2%) with metastatic breast cancer were postmenopausal.

Histologic grade 2 was most common (Table 6).

Histologic grade 1 was significantly more encountered in operable tumors (8.2%) compared to locally advanced and metastatic disease (0%) (x^2=5.2; p<0.01). Grade 2 was most frequent in operable tumors and approximately equally present in locally advanced and metastatic disease (60.3 vs. 57.1%) (x^2=3.1; p>0.05). Grade 3 was least common in operable disease (21.7%) and in metastatic tumors (42.9%) (x^2=3.1; p>0.05).

Nuclear tumor grades 2 and 3 were most common (Table 7).

Nuclear grade 1 in operable tumors was significantly more common (6.7%), compared to locally advanced and metastatic disease (0%) (Mantel-Haenszel=4.1; p<0.05).

Nuclear grade 2 was most common in operable tumors (62.4%) and almost equally distributed in locally advanced and metastatic disease (58.7 vs. 35.7) (x^2=1.16; p>0.05).

Nuclear grade 3 was the rarest finding in operable disease (30.9%) and most common in metastatic disease (64.3%) (x^2=0.04; p>0.05).

Ductal carcinoma was the most common histology (71.2%), and carcinoma *in situ* the rarest (0.9%) (Table 8).

Ductal carcinoma was found in 74.4% of operable tumors, and was the least common in patients with metastatic disease (57.3%) (x^2=1.2; p>0.05). Lobular carcinoma was almost equally distributed between operable and locally advanced disease (11.7 vs. 13.4%), with somewhat lower frequency in metastatic disease (6.3%) (x^2=0.84; p>0.05). Ductal-lobular carcino-

Table 6. Clinical TNM stages in relation to histologic grade

	Clinical TNM stages								
Histologic grade	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Number of patients								
1	0	15	11	1	1	0	0	0	28 (6.6)
2	0	60	84	46	53	21	17	8	289 (68.7)
3	0	9	27	19	18	17	8	6	104 (24.7)
Total	0	84	122	66	72	38	25	14	421 (100)

Table 7. Clinical TNM stages in relation to nuclear grade

	Clinical TNM stages								
Nuclear grade	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Number of patients								
1	0	12	7	2	2	0	0	0	23 (5.5)
2	0	56	78	38	42	21	16	5	256 (60.9)
3	0	16	36	26	28	17	9	9	141 (33.6)
Total	4	84	121	66	72	38	25	14	420 (100)

Table 8. Clinical TNM stages in relation to histopathologic types of tumors

	Clinical TNM stages								
Histopathologic types	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Number of patients								
Ductal	0	61	94	53	54	29	18	11	320 (71.2)
Lobular	0	14	15	5	7	6	5	1	53 (11.7)
Ductal-lobular	0	10	15	8	11	7	2	2	55 (12.4)
Carcinoma *in situ*	4	0	0	0	0	0	0	0	4 (0.9)
Mastitis carcinomatosa	0	0	0	0	0	14	1	2	17 (3.8)
Total	4	85	124	66	72	56	26	16	449 (100)

Table 9. Breast cancer receptor status combinations related to clinical disease stages

Stage	*ER+/PR+ n (%)*	*ER+/PR- n (%)*	*ER-/PR+ n (%)*	*ER-/PR- n (%)*	*Total n (%)*
Operable	207 (59.8)	49 (14.1)	16 (4.6)	74 (21.5)	346 (78.6)
Locally advanced	33 (3.7)	13 (16.2)	4 (42.6)	30 (37.5)	80 (18.2)
Metastatic	6 (42.8)	3 (21.4)	0	5 (35.8)	14 (3.2)
Total	246	65	20	109	440

ma was almost equally distributed among these three groups (12%), while mastitis carcinomatosa was slightly more common in locally advanced compared to metastatic disease (x^2=0.84; p>0.05).

ER/PR status was determined in 440 (98%) women: ER+/PR+ was observed in 246 (54.7%), ER+/PR- in 65 (14.5%), ER-/PR+ in 20 (4.5%), and ER-/PR- in 109 (24.3%) women. ER+ breast cancer status was 3-fold higher than ER- status.

The breast cancer receptor status in relation to clinical disease stage is shown in Table 9.

HER2 receptor status was determined in 94 patients. Nine of these had weak positivity (+), 10 moderate (++) and there were 75 women with strong positivity (+++).

The percentage of HER2 positive findings (+++) related to ER status is shown in Table 10. HER2 positive patients were most commonly ER-, while HER2 negative women were most commonly ER+ (p<0.01).

Table 11 depicts HER2 status (+++) and clinical stage of primary breast cancer.

The upper lateral quadrant was the most common primary tumor site (Table 12).

Central tumor localization was similar for locally advanced and metastatic carcinoma (33 vs. 25%), and rarest in operable tumors (14%) (x^2=9.1; p<0.01). Incidences of other tumor sites did not differ significantly among different clinical disease stages.

Left breast was more commonly involved (Table 13). There was no statistically significant difference in left vs. right breast involvement in different clinical disease stages.

Radical surgery was the most common type of operation (Table 14). A significant difference in the type of surgery related to clinical disease stage was demonstrated (F=37.8, p<0.01). Radical operations were more

Table 10. HER2 overexpression and/or amplification (+++) related to steroid receptor level in primary breast cancer

Status	*HER2 positive n (%)*	*HER2 negative n (%)*	*Total n (%)*
ER positive	13 (35.2)	24 (64.8)	37 (100)
ER negative	28 (73.7)	10 (26.3)	38 (100)
Total	41	34	75

p<0.01

Table 11. HER2 status (+++) and clinical stage of primary breast cancer

Clinical stage	*HER2 positive n (%)*	*HER2 negative n (%)*	*Not done Total n (%)*	*n (%)*
Operable	23 (53.5)	20 (46.5)	303 (87.6)	346 (78.6)
Locally advanced	13 (52)	12 (48)	55 (88)	80 (18.2)
Metastatic	5 (71.4)	2 (28.6)	7 (51)	14 (3.2)
Total	41	34	365	440

Table 12. Clinical stage and primary tumor site

Site	*Clinical stages*								
	0	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Number of patients								
Central	2	14	12	9	13	23	4	4	81 (18)
ULQ[1]	2	57	67	37	38	24	14	8	247 (55.1)
UMQ[2]	0	8	23	14	14	6	3	1	69 (15.4)
LLQ[3]	0	2	10	3	4	2	3	1	25 (5.6)
LMQ[4]	0	3	10	3	3	1	2	2	24 (5.3)
Axilla	0	1	1	0	0	0	0	0	2 (0.4)
Areolar	0	0	1	0	0	0	0	0	1 (0.2)
Total	4	85	124	66	72	56	26	16	449 (100)

[1]upper lateral quadrant, [2]upper medial quadrant, [3]lower lateral quadrant, [4]lower medial quadrant

Table 13. Clinical stage and involved breast

Involved breast	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Clinical stages								
	Number of patients								
Right	0	36	62	30	31	26	12	9	206 (45.9)
Left	4	49	62	36	41	30	14	7	243 (54.1)
Total	4	85	124	66	72	56	26	16	449 (100)

Non-significant for all parameters

Table 14. Type of operation and clinical disease stage

Type of operation	*0*	*I*	*IIA*	*IIB*	*IIIA*	*IIIB*	*IIIC*	*IV*	*Total n (%)*
	Clinical stages								
	Number of patients								
Radical	4	69	108	56	72	23	5	2	339 (75.5)
Conservative	0	16	16	10	0	0	0	0	57 (12.7)
Biopsy	0	0	0	0	0	34	20	14	53 (11.8)
Total	4	85	124	66	72	57	25	16	449 (100)

commonly utilized in lower disease stages and biopsies were more common in higher disease stages.

Radical interventions were more commonly performed for operable tumors (88.1%), while biopsies were significantly more common in metastatic disease (88.1%) and locally advanced tumors (66.2%).

Discussion

Breast cancer is the most common malignant neoplasm in women in Serbia, with great significance because of the continual rise of its incidence and mortality. It is the leading cause of death from malignant diseases, one of the causes of premature death in female population, usually detected in advanced stages and with unfavorable age distribution [2,3].

At the Institute of Oncology and Radiology of Serbia (IORS) [4], according to the hospital registry, the average age at breast cancer diagnosis was 56 years, with 30% of women below 50 years of age (6% below 40 years; 24% aged 40-49 years). According to the data for central Serbia for 2004 [5], breast cancer was diagnosed before 50 years of age in 22% of women (5% below 40; 17% aged 40- 49 years). Our patients were 56 years old on average, but there were 32.5% of women below 50 years of age and 8.2% of those below 40. This age distribution is less favorable compared to other countries in view of early age at diagnosis, despite late detection of breast cancer. The average age of the affected in the USA, Australia, and Slovenia is around 60 years (63 in the USA; 61 in Australia, 61 in Slovenia) [2]. In Croatia and Great Britain, breast cancer was diagnosed below 50 years of age in 19.5% (4.5% below 40; 15% in the age range from 40 to 49 years) [5].

There were significantly more women in postmenopause at the time of diagnosis, confirming the literature data [6].

According to the IORS data, only 38% of breast cancer cases are detected as a locally confined disease, while 9% of women already have distant metastases at the time of diagnosis [4]. According to the available data from other countries, the percentage of localized disease among new breast cancer cases is 2-fold higher. In France, owing to their screening program, 70% of breast cancers are detected as a local disease. In their analysis, Hill et al. [7] reported that localized breast cancer was found in 69% of women in America, locally advanced breast cancer in 25.4%, while metastatic disease was present in 4.9% of women. In our study, 62% had local disease at the time of diagnosis, 34% had locally advanced disease (operable locally advanced in 16%), while metastatic disease was identified in 3.6% of women. Such results can perhaps be explained by the small sample and the fact that 61.4% of women were urban dwellers, with somewhat higher level of health education.

The percentages of particular TNM clinical stages in our investigation demonstrated that most patients had stage II disease at the time of diagnosis [8]. Comparing our results with the results of the IORS [4], similar distribution was established for 0, I, II and IV clinical stages, with the discrepancy for stage III (34 vs. 16%).

According to the IORS data [4], only 1% of women are admitted with non-palpable, *in situ* breast tumors detected by mammography. Out of palpable tumors, one

fifth of tumors are up to 2 cm in size - T1 (21%), T2 tumors (2-5 cm) occur in 47%, T3 tumors (> 5 cm) occur in 7%, and T4 tumors in 24% of women. In this study, similar to IORS TNM stage distribution of primaries was found: Tis in 0.9%, T1 in 14%, T2 in 49.3%, T3 in 6.2%, and T4 in 14% of the studied cases. T2 tumors were most common in patients with operable breast carcinoma, with most cases in stage IIA with unfavorable relationship with T1 tumors (26.2 vs. 9.1%). This distribution is unfavorable compared to other authors' findings [9-11]. Owing to screening, better and timely diagnosis in developed countries, tumors are detected in around 30% of cases in their *in situ* stage, while tumors up to 2 cm in size are detected in over 70% of women [2].

In our study, there were 44% of women with negative lymph nodes, while 12% of women had an unknown number of involved lymph nodes. In 20% of women 1-3 lymph nodes were positive, in 18% 4-9 lymph nodes, and 6% of cases had over 10 positive lymph nodes. In 0.7% of the cases sentinel node metastases were found. The results of our study differ from other authors' results [9,12]. In various studies, negative nodal status is more common than in our study (around 60%), with significantly less cases in N2 (around 10%) and N3 (around 5%) stages, which could also be explained by better and timely diagnosis of breast cancer in developed countries.

In around 10% of patients with newly diagnosed breast carcinoma, the disease is diagnosed in its metastatic phase. Breast cancer most commonly metastasizes to the bones (30-40%), lungs (15-25%), liver (5-22%), pleura (8%), central nervous system (4%) and multiple organ metastases are found in 25-50% of breast cancer cases [13]. In our study, the most common single organ site of metastases was the liver (19%) of those with metastatic disease, while bones were affected in 12% of the cases. The most common combination of metastatic sites was the liver and bones.

Histologic and nuclear tumor grades are a reliable predictor of the malignant potential of breast cancer. Histologic and nuclear grade 2 was the most common, while grade 1 was the rarest finding. Our results, regarding these tumor parameters confirmed the literature data [9,12,14].

According to the literature data, ductal carcinoma occurs in up to 80% of the cases, lobular carcinoma in 5-10%, while DCIS accounts for 10-20% of all breast carcinomas and 80% of all non-infiltrating *in situ* carcinomas [13]. Most of our patients had ductal carcinoma [8], while lobular and ductal-lobular carcinomas were found in around 12% of women. In contrast to other authors [12,15-17], the rarest entity in our study was *in situ* carcinoma (0.9%), which could be explained by the absence of programs for early detection and screening programs in our country in contrast to developed countries worldwide.

Around 70% of all breast primaries express ER, while 30% are ER- [18], which is not much different from our results. Several studies have reported a lower percentage of ER+ expression, 36.1% [19] and 32% [20].

Around 70-80% of those with receptor-positive disease will respond favorably to hormonotherapy; the remaining 20-30% will be resistant. The background of such therapeutic response could be the existence of various ER/PR combinations, i.e. different concentrations of these receptors. In the European population there were 50% of ER+/PR+ cancers, 25% were ER-/PR-, 20% were ER+/PR-, and around 5% were ER-/PR+ [21].

There is a significant association of amplification/overexpression of HER2 and low ER and PR concentrations [22,23], which is in concordance with our results. Overexpression of the receptor is associated with poor prognosis in patients with breast cancer [23].

Left breast was more commonly affected, while tumors were most commonly situated in the upper lateral quadrant and central region [18]. The distribution of the primary tumor sites in our study corresponded to the literature data [8]. Central tumor site was more common in locally advanced and metastatic disease compared to operable carcinoma, thus explaining the biologic aggression and poor prognosis of centrally situated tumors.

Organized breast cancer screening has contributed to the increase of number of newly detected breast carcinoma in its early stage, meaning that an increasing number of patients is eligible for conservative surgery. In developed countries, the percentage of conservative surgical interventions has increased from around 25% to 60-70% [19]. In this study, radical surgery was applied to 75% of women, while conservative in 13% only.

Conclusion

In view of the unfavorable age of patients at the time of diagnosis and clinical and biological tumor characteristics, the results of this study confirmed that it is of vital importance to provide breast cancer prevention, including breast cancer screening, and to organize breast cancers units according EUSOMA guidelines.

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