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Original contributions

Effectiveness of surgical treatment and the analysis of prognostic factors in mucinous carcinoma of the breast

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Objective. The aim of the study was to determine the populational and clinical features of mucinous breast carcinoma, to determine specific features of mucinous breast carcinoma by immunohistochemical evaluation, to assess prognostic factors, with special consideration to MIB-1 proliferation factor, as well as p53 gene and c-erb B2 expressions, to assess the effectiveness of operative treatment and the causes of its failure and to determine the optimal method of adjuvant therapy.
Material. The group of 81 patients with mucinous breast carcinoma who received initial surgery between 1952 and 1993 was studied. The age was 30-84, mean 62. The duration of symptoms ranged from 1 to 35 months, mean 8. Fifty patients (61.7%) presented the pure and 31 patients – (38.3%) mixed type of carcinoma.
Results. The actuarial 10-year overall and symptom-free survival was 60.5% (74.0% for pure and 39.0% for mixed type of cancer). Statistically significant better chance of 10-year survival without cancer was observed in women over sixty years of age, menopausal or postmenopausal, with no involvement of axillary nodes, in stage I and IIA, with lump size under 4 cm, microscopically negative axillary nodes, and pure mucinous type. Patients whose tumours did not present p53 expression, had statistically significant better chance of disease–free 10-year survival. In the sub-group of 50 patients with pure type carcinoma, statistically significant better disease–free 10-year survival was obtained in patients with clinically and microscopically negative axillary nodes, and whose tumours revealed no p53 expression. In the sub-group of 31 patients with mixed type carcinoma, statistically significant chance of 10-year survival without cancer was observed in patients over sixty, menopausal or postmenopausal. None of the immuno-histochemically evaluated discriminants showed statistically significant impact on disease-free survival in this group. The following factors in the entire group of patients were responsible for statistically significant, unfavourable impact on 10- year survival without cancer: mixed type, age below 60, and clinical axillary involvement. In the group of patients with pure type carcinoma, statistically significant, unfavourable influence on 10-year disease-free survival was exerted solely by the clinical presence of N2 metastases to axillary nodes. In the group of patients with mixed type, only the patients' age <60 had an unfavourable effect on 10-year survival without cancer. The specific populational and clinical features of mucinous breast carcinoma were: mean age – 62 years (30-84), over 3/4 of patients being menopausal or postmenopausal, mean time of symptoms duration – 8 months (1-36), most common localisation of tumour in the outer quadrants of the breast, lump size in the breast (pT) not exceeding 4 cm, in over 70% of patients, microscopically negative axillary nodes in over 60% of patients. The specific features found by immunuhistochemical evaluations were: relatively low MIB-1 index which in over half of the patients did not exceed 14 (2-46), over 90% of patients being oestrogen receptor positive and over 60% – progesterone receptor positive, low percentage of tumours presenting p53 and c-erb B2 expression – 12.3% and 9.9% respectively.
Conclusions. Independent, unfavourable prognostic factors in patients with mucinous breast carcinoma are: age below 60, clinically established presence of axillary metastases and the mixed type of disease. Surgical treatment allows to obtain over 60% of 10-year cancer free survival in patients with mucinous carcinoma of the breast, of which 74% in the pure, and 39% in the mixed mucinous type group. The basic cause of treatment failure is generalisation of the malignant process. All patients with mixed mucinous breast carcinoma type and those with pure mucinous type who are axillary positive should receive the same treatment as patients with ductal infiltrating carcinoma at the corresponding stage of clinical advancement, both local and adjuvant. For patients with pure mucinous breast carcinoma type and negative axillary nodes, breast conservation treatment should be the main option, eventually without adjuvant systemic therapy.

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An abbreviated Ph.D. thesis

Analiza skuteczności leczenia chirurgicznego oraz czynników prognostycznych u chorych na śluzowatego raka sutka

Wstęp. Rak śluzowaty sutka (RSS) stanowi wg różnych autorów 1-5% nowotworów złośliwych sutka. Wyróżnia się dwie postacie histologiczne RSS: czystą oraz mieszaną. RSS jest powszechnie zaliczany do grupy tzw. „lepiej rokujących" postaci raka sutka.

Cel pracy. Określenie charakterystycznych cech populacyjnych i klinicznych RSS, określenie charakterystycznych cech RSS w dostępnych badaniach immunohistochemicznych, ocena czynników prognostycznych u chorych na RSS, ze szczególnym uwzględnieniem: wskaźnika proliferacji MIB-1 i ekspresji genu p53 i c-erb B-2, ocena skuteczności leczenia chirurgicznego i przyczyn jego niepowodzenia, próba określenia optymalnego sposobu leczenia adiuwantowego chorych na RSS.

Materiał. Przedmiotem szczegółowej analizy jest grupa 81 chorych na RSS, leczonych pierwszorazowo chirurgicznie w COOK w okresie 1952-1993 r. Najmłodsza chora liczyła 30 lat, najstarsza 84 lata, średni wiek wynosił 62 lata. Czas trwania objawów chorobowych wahał się od 1-35 miesięcy, średnio wynosił 8 miesięcy. U 50 chorych (61,7 %) rozpoznano czystą, a u 31 (38,3 %) mieszaną postać RSS.

Wyniki. W badanej grupie 81 chorych na RSS prognozowane 10-letnie przeżycie całkowite i bezobjawowe wyniosło 60,5%, na czystą postać 74,0 %, na postać mieszaną 39,0 %. Statystycznie znamienne wyższe szanse bezobjawowego 10-letniego przeżycia mają chore: powyżej 60 roku życia, w trakcie i po menopauzie, bez klinicznie podejrzanych węzłów chłonnych pachy, w I i II A stopniu zaawansowania raka wg TNM, z guzem w sutku (pT) nie przekraczającym 4 cm, mikroskopowo bez przerzutów w węzłach chłonnych pachowych, z czystą postacią RSS. Statystycznie znamiennie wyższą szansę bezobjawowego 10-letniego przeżycia miały chore, u których guz nie wykazywał ekspresji genu p53. W grupie 50 chorych na czystą postać RSS statystycznie znamienne wyższe bezobjawowe 10-letnie przeżycie uzyskano u chorych: bez klinicznie podejrzanych węzłów chłonnych w pasze i bez mikroskopowo stwierdzonych przerzutów w tych węzłach oraz u chorych, u których guz nie wykazywał ekspresji genu p53. W grupie 31 chorych na mieszaną postać RSS statystycznie znamiennie wyższą szansę bezobjawowego 10-letniego przeżycia miały chore powyżej 60 roku życia i w trakcie lub po menopauzie. Żaden ze wskaźników badanych immunohistochemicznie nie wykazał statystycznie znamiennego wpływu na przeżycie bezobjawowe w tej grupie. W całej badanej grupie chorych znamienny statystycznie, niekorzystny wpływ na 10-letnie przeżycie bezobjawowe w wielocechowym modelu Coxa, miały: mieszana postać RSS, wiek chorych poniżej 60 roku życia i klinicznie stwierdzona obecność przerzutów w węzłach chłonnych pachowych. W grupie chorych na czystą postać RSS, znamienny statystycznie, niekorzystny wpływ na 10-letnie przeżycie bezobjawowe w wielocechowym modelu Coxa ma jedynie klinicznie stwierdzona obecność przerzutów do węzłów chłonnych pachowych o zaawansowaniu N2. W grupie chorych na mieszaną postać RSS, znamienny statystycznie, niekorzystny wpływ na 10-letnie przeżycie bezobjawowe, w wielocechowym modelu Coxa, ma jedynie wiek chorych poniżej 60 roku życia. Charakterystyczne cechy populacyjne i kliniczne RSS, stwierdzone w badanej grupie chorych to: a) średni wiek 62 lata (30-84), b) ponad 3/4 chorych w trakcie i po okresie menopauzy, c) średni czas trwania objawów chorobowych 8 miesięcy (1-36), d) najczęstsza lokalizacja guza w kwadrantach zewnętrznych sutka, e) u ponad 70% chorych guz w sutku (pT) nie przekraczający 4 cm, f) u ponad 60% chorych mikroskopowo stwierdzony brak przerzutów w węzłach chłonnych pachowych. Charakterystyczne cechy RSS w wykonanych badaniach immunohistochemicznych to: a) stosunkowo niski wskaźnik MIB-1, u ponad połowy chorych nie przekraczający 14 (2-46), b) u ponad 90% chorych obecność receptora estrogenowego i u ponad 60% progesteronowego, c) niski odsetek guzów wykazujących ekspresję genu p53 i c-erb B2, odpowiednio 12,3% i 9,9%.

Wnioski. Niezależnymi, niekorzystnymi czynnikami prognostycznymi u chorych na RSS są: wiek chorych poniżej 60 roku życia, klinicznie stwierdzona obecność przerzutów w węzłach chłonnych pachowych oraz mieszana postać RSS.

Leczenie chirurgiczne pozwala na uzyskanie ponad 60% 10-letnich przeżyć bezobjawowych u chorych na RSS, w tym 74% w grupie chorych na czystą i 39% na mieszaną postać RSS. Podstawową przyczyną niepowodzenia leczenia jest uogólnienie procesu nowotworowego.

Wszystkie chore na mieszaną postać RSS oraz chore na czystą postać RSS z przerzutami do węzłów chłonnych pachowych winny być leczone tak samo, jak chore na RPN, w odpowiednim stopniu zaawansowania klinicznego, zarówno miejscowo, jak i uzupełniająco.

U chorych na czystą postać RSS, bez przerzutów do węzłów chłonnych pachowych, należy przede wszystkim rozważyć leczenie chirurgiczne, oszczędzające sutek i ewentualnie rezygnację z adiuwantowego leczenia systemowego.

Key words: mucinous carcinoma of the breast, prognostic factors, cancer free survival
Słowa kluczowe: rak śluzowaty sutka, czynniki prognostyczne, przeżycia bezobjawowe

Introduction

According to many authors, mucinous carcinoma constitutes 1-5% of malignant tumours of the breast [1-17). Mucinous carcinoma of the breast is a disease of women, although rare cases of its appearance in males have been reported.

There is a prevailing opinion that mucinous carcinoma is found in older women, when compared with other microscopically detected breast cancers [1, 2, 4, 8-10, 18-

-20]. Berg and Hutter, basing on the data obtained from the SEER (Surveillance, Epidemiology and End Results) Register of the American National Cancer Research Institute, showed that the mean age of patients with mucinous carcinoma of the breast exceeded by 9-11 years the mean age of patients with infiltrating ductal carcinoma, and that the prevalence of mucinous carcinoma of the breast grew dramatically in women over 60 years of age. Rosen et al. found that it constituted 1 % in the group of cancer patients below 35 years of age, and 7% in those over 75 years of age.

According to the definition of the World Health Organisation, mucinous carcinoma of the breast is a malignancy containing a large amount of extracellular mucin visible on gross examination which is also present within the cancerous cells. In English language literature, the term most commonly used in relation to this malignancy is "mucinous carcinoma" although other terms, such as "gelatinous", "colloid, ‚mucous' or ‚mucoid carcinoma' are also applied [8, 10, 20].

Two types of mucinous carcinoma of the breast have been described: pure and mixed. The pure type involves tumours which are fully built of isolated small islands of continuous cancerous tissue ‚floating' in abundant extracellular mucin. Mixed type tumours, have additional areas of infiltrating carcinoma with no extracellular mucin present [4, 8-10, 20, 22]. Mucinous carcinoma of the breast was first described in 1826 and we owe detailed evaluation of its microscopic features and clinical outcome to such authors as: Robinson (1852), Larey (1853), Lange (1896), Gaabe (1908), Halsted (1915), Geschickter (1930 and 1938), Saphir (1941) [6].

In 1980, Capella et al. made an attempt at subtyping mucinous carcinoma of the breast, and distinguished three types: type A-built of cancerous cells slightly more pleomorphic than type B, arranged in small groups floating in abundant extracellular mucin, and routinely with the absence of mucin within the cells; type B-built of more monomorphic cancerous cells, arranged in larger clusters, with smaller amount of extracellular mucin, but with the occasional presence of mucin within the cells; the overwhelming majority of B-type tumours being argentophilic; type AB, sharing the characteristics of the other two and the rarest of the three [2, 6, 9, 20, 23]. The investigations by Scopsi et al. Showed, however, that this division is of no prognostic significance, while such significance is provided by the division into pure and mixed types [2, 8, 9, 24].

Mucinous breast carcinoma generally counts among the ‚better prognosing' types of breast cancer [2, 8, 9, 20, 22, 25]. Particularly good prognosis is associated with pure type [1, 2, 4, 10, 23, 24, 26-29], where metastases to regional lymph nodes are uncommon (8, 10, 20) and long term survival reaches, and even exceeds 90% [4, 24, 30-32]. Better prognosis in the group of women with pure mucinous carcinoma type in comparison with infiltrating ductal carcinoma patients, has been also proved in a number of indirect observations. Toikkanen et al., found that in the group of women with breast cancers who survived 10 years, there was a higher percentage of mucinous carcinoma cases, as compared to the entire population. In the group of women who were alive 20 years after treatment, Mituś et al. found a higher percentage of mucinous carcinoma cases (9.4%) as compared with a model group of breast cancer patients presented by Henderson (2.4%). Both Toikkanen et al. and Dixon et al. stress that 10 years after surgery, late recurrence of mucinous carcinoma is much rarer than of infiltrating ductal carcinoma of the breast [27]. Andersen et al. reported higher percentage of mucinous carcinoma of the breast among disease-free patients in whom breast cancer was screened, as compared to the entie population.

According to a majority of authors, the clinical outcome and prognosis in the mixed type of mucinous carcinoma of the breast were similar as in the infiltrating ductal carcinoma [8, 22].

A detailed histological examination is obviously of basic importance for diagnosing mucinous carcinoma of the breast. Fine needle aspiration biopsy is generally a highly useful method of detecting breast cancers, and among them, mucinous breast carcinoma [4, 20, 21, 34, 35]. Nevertheless, in order to obtain detailed characteristics of a tumour and to distinguish the pure or mixed type of mucinous carcinoma of the breast, not only intraoperative cryo-evaluation but also postoperative histologic assessment is necessary [4, 20, 35].

Visualising examinations are of supportive value in diagnosing mucinous carcinoma of the breast [4, 20, 36, 37, 38]. On ultrasound imaging, mucinous breast carcinoma usually presents as a well defined round or oval mass with hypogenous echo pattern [37]. Mammography generally visualises a single round or oval mass of lobular structure [36]. In the pure form the mass is well defined, and in the mixed type its contour is commonly irregular [4]. Calcium deposits are found in 20-40% of patients [20, 37].

Objective of the study

- To determine specific population and clinical features of mucinous breast carcinoma,
- To determine specific features of mucinous breast carcinoma in available immunohistochemical evaluations,
- To assess the prognosticators in mucinous breast carcinoma patients, with special consideration to MIB-1 proliferation factor as well as p53 gene and c-erb B2 expressions,
- To assess the effectiveness of operative treatment and of the causes of its failure,
- To determine the optimum method of adjuvant therapy in patients with mucinous breast carcinoma.

Methods

The methodics have been based on a retrospective analysis of the clinical material involving 81 patients with mucinous carcinoma of the breast who had received initial surgical treatment at the Cracow Branch of the Oncology Centre from 1952 to 1993.

The basic data about the patients was obtained from clinical records, but other sources such as letters referring patients

for treatment, case reports from other therapeutic institutions, and letters written by patients or their families have also been used. Information on the date of death was obtained, in writing, from families or state agencies dealing with population statistics. The follow-up covered 100% of patients.

Over the above mentioned period of time, 3740 women with breast cancer received initial surgical treatment in the Cracow Branch of the Oncology Centre. 81 of them, i.e. 2.2%, were diagnosed with mucinous carcinoma of the breast. The microscopic status of all tumours was reanalysed in detail. In each case, a histological diagnosis of mucinous carcinoma was based on the criteria complying with the WHO classification. On microscopic assessment of tumour specimens pure and mixed types of mucinous carcinoma were distinguished. Typed as pure, were tumours showing no presence of infiltrating ductal carcinoma component (or lobular infiltrating carcinoma) following the criteria suggested by Norris and Taylor. Typed as mixed, were all tumours in which, apart from mucinous carcinoma, there was additional presence of infiltrating ductal or lobular lesions. In none of the studied cases did the additional infiltrating carcinoma component exceed 75% of the tumour section surface.

The clinical advancement of tumour in the studied group was evaluated according to 1997 UICC TNM system. Patients in this group were currently staged in respect of disease advancement according to the presently adopted TNM classification of breast cancer. For the needs of this thesis the staging was expressed in the system in use since 1997. All patients received initial surgical treatment at the Cracow Branch of Oncology Centre and it was here that an accurate microscopic analysis of the material obtained at surgery was performed. All other therapeutic procedures, such as postoperative irradiation and/or chemo-hormonotherapy were given in the same institution.

A detailed assessment of the clinical outcome of mucinous carcinoma of the breast was made and clinical outcomes as well as treatment results of pure and mixed types were compared. Specific features of mucinous carcinoma of the breast were determined in the available immunohistochemical evaluations. In order to specify the prognostic factors in a given group of patients, an analysis was performed to find how the treatment results depended on population, clinical and microscopic characteristics, as well as on the presence of hormonal receptors, MIB-1 proliferation index, expression of p53 and c-erb B-2. The choice of the last three indices resulted, first of all, from the data contained in literature, suggesting or pointing to their prognostic value in malignant tumours in humans (particularly those including, obviously enough, patients with breast tumours) and second, from the availability of the Cancer Pathology Department of the Cracow Branch of the Oncology Centre for making the required determinations [39-41].

Immunohistochemical determinations of the content of MIB-1 proliferative antigen and the product of *p53*, *c-erb B2* as well as hormonal receptors in paraffin embedded preparations, were performed in the Immunohistochemistry Laboratory of the Cancer Pathology Department of the Oncology Centre.

Statistical analysis

The criterion of treatment effecacy was a disease-free 10-year survival, counting from the date of operation. All patients were followed up for at least five years, decease being the sole reason for termination of follow-up. The mean follow-up time was 15 years (5-46). The probability of 10-year survival was assessed by the Kaplan-Meier method. Log-rank test according to Peto et al. was used to assess the differences found in the material. P values ≤ 0.05. were considered statistically significant.

To assess the effect of the selected factors on the patients' survival, Cox proportional hazard model was used [42]. At the first stage, the influence of the analysed factors was assessed using monovariate Cox model. For factors, the level of which was divided into more than two classes having natural sequence (i.e. tumour advancement acc. to TNM), the significance of relative risk trend was also investigated. At the next stage, multivariate analysis in reference to disease-free survival was performed, with consideration to population, clinical and microscopic factors as well as those evaluated by immunohistochemistry.

The final selection of the set of prognostic factors was made with the backward regression method. The effect power of the studied prognostic factors was presented in the form of a relative hazard risk.

Many variables included in the study are of continuous nature (i.e. age, size of tumour in the breast etc.) Therefore, first, the Cox models were constructed which considered a given variable in a continuous aspect, and next, optimum potential cut points were looked for. For this purpose, two survival curves were compared, representing values above and below the cut point. The discriminative power of the cut point was measured by the value of test probability p, of the log rank test comparing the two curves.

Material

The subject of detailed analysis was a group of 81 patients with mucinous carcinoma of the breast who had received primary surgical treatment atthe Cracow Branch of Oncology Centre from 1952 to 1993. The youngest patient was 30 years old and the oldest 84; the mean age was 62 years. The time of symptom duration ranged from 1 to 35 months, with a mean value of 8 months. Pure type was found in 50 (61.7%) and mixed in 31 (38.3%) of patients. In terms of statistics, women with pure type of mucinous carcinoma of the breast were significantly older than those with mixed type and presented significantly less common involvement of the axillary nodes. In the studied group, the risk of positive axillary nodes was in direct correlation with the size of tumour.

In the group of patients with tumours under 2 cm, positive axillary nodes were found in 4.3% of patients, while in the group with tumours over 4 cm, in as many as 91.7% of patients. The observed differences are highly statistically significant (log rank test $p<0.01$). It should be noted that among 15 patients with pure mucinous carcinoma type and tumour size not exceeding 2 cm, none was node positive. In 43, i.e. 53.1% of patients, the MIB-1 index was below or equal 14, and in the remaining 38, i.e. 46.9%, it exceeded this value. Expression of *p53* and *c-erb B2* was rare; it was found only in 12.3% and 9.8% of patients respectively. 74 i.e. 91.4% of patients were positive for oestrogen receptor and 51, i.e. 63% of patients for progesterone receptor.

Comparing the two groups of patients, those with pure type and those with mixed type, it has been found that:

- tumours with *p53* and *c-erb B2* expression were equally rare in both groups,
- the presence of progesterone receptor was slightly, though not significantly, more frequent in patients with pure type,
- among 31 patients with mixed type, the MIB-1 index exceeding 14, was presented by 19 i.e. 61.3% tumours, while among 50 patients with pure type – 19 i.e. 38% tumours; this difference is statistically significant (log-rank-test $p<0.05$),
- among 31 patients with mixed type, the presence of oestrogen receptor was found in 25, i.e. 80.6% tumours, whereas among 50 patients with pure type – in 49, i.e. 98% tumours; this difference is also statistically significant (log-rank-test $p<0.01$).

Results

In the studied group of 81 patients with mucinous carcinoma of the breast, the overall actuarial 10-year survival without cancer was 60.5%, as shown in Figure 1.

The actuarial 10-year cancer free survival in patients with pure type of mucinous carcinoma of the breast was

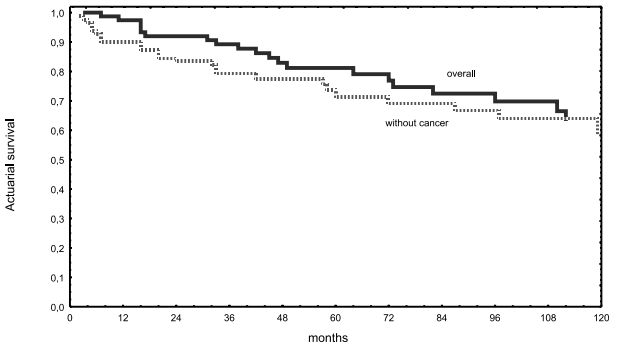

Figure 1. Actuarial overall and cancer free 10-year survival

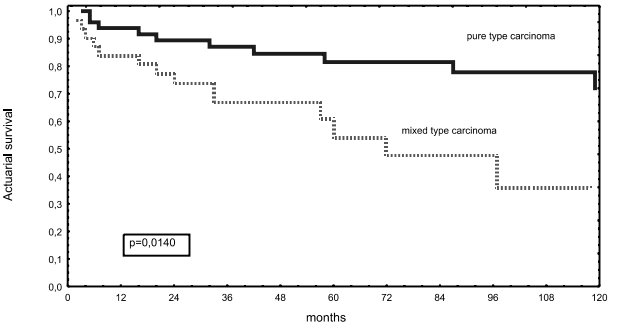

Figure 2. Cancer free survival by microscopic type of mucinous carcinoma of the breast

74.0% and in those with mixed type – 39.0%, as shown in Figure 2.

Statistically significant higher chance of 10-year survival without cancer is observed in patients: over 60 years of age, menopausal or postmenopausal, without presence of clinically suspected axillary lymphatic nodes, in stages I and II A of tumour advancement according to TNM, with mass size in the breast not exceeding 4 cm, no microscopically detected metastases to axillary lymph nodes, and with pure type of mucinous carcinoma of the breast. A statistically significant higher chance of 10 year survival without cancer was observed in patients with the absence of *p53* gene expression.

Table I presents treatment results in a group of 50 patients with pure type of mucinous carcinoma of the breast by chosen population and clinical characteristics.

Table I shows that in a group of 50 patients with pure type of mucinous carcinoma of the breast, a statistically significant higher 10-year cancer-free survival was obtained in patients with no clinically suspected axillary node involvement and with microscopically negative nodes. All 15 patients with pT not exceeding 2 cm, and with no axillary node involvement *survived for 10 years without cancer.*

The results of treatment by MIB-1 index, p53 and c-erb B2 expression, and presence of hormonal receptors in

Table I. The results of treatment of 50 patients with "pure" mucinous carcinoma of the breast, and selected populational and clinical characteristics

Population or clinical characteristics	No. of treated patients	Actuarial of 10-year cancer free survival in%	p (log-rank test)
* age:			
under 50	8	68.6	
51-60	8	72.9	
over 60	34	71.7	0.8304
* menopausal status:			
premenopausal	9	60.0	
menopausal and postmenopausal	41	74.4	0.0861
Localisation of tumour in the breast			
Outer quadrants	26	74.9	
Other parts of the breast	24	70.4	0.5006
*clinical nodal status (N):			
N0	23	80.9	
N1	20	65.0	
N2	7	34.3	0.0018
*tumour grading acc. to TNM:			
I°+ II°A	21	83.6	
II°B	12	75.0	
III°	17	61.3	0.1913
Size of mass in the breast assessed by a pathologist in operation material (pT):			
Up to 4 cm	36	78.4	
Over 4 cm	14	64.3	0.3433
* microscopic nodal status (pN):			
pN0	35	87.8	
pN+(1-3)	8	45.7	
pN+(>3)	7	42.9	0.0021
Total	50	74.0	

* statistically significant differences, log-rank test, $p<0.05$

Table II. The results of treatment of 50 "pure type" patients and immunohistochemical evaluations

Discriminants	No. of treated patients	Actuarial 10-year cancer free survival	p (log-rank-test)
MIB-1 index			
≤14	31	77.4	
>14	19	68.4	0.6542
* *p53* gene expression			
yes	6	33.3	
no	44	78.9	0.0257
c-erb B2 gene expression:			
yes	4	75.0	
no	46	71.0	0.9393
Oestrogen receptor:			
present	49	70.2	
absent	1	–	0.2758
Progesterone receptor:			
present	34	68.7	
absent	16	67.0	0.7915

*statistically significant difference

a group of patients with pure type of mucinous breast carcinoma are presented in Table II.

Table II shows that statistically a significant higher chance of 10- year cancer-free survival was observed in patients with pure type of mucinous carcinoma of the breast, and no *p53* gene expression.

Table III shows treatment results in a group of 31 patients with mixed type of mucinous carcinoma of the breast, by selected population and clinical characteristics.

Table III shows, that in a group of 31 patients with mixed type of mucinous carcinoma of the breast, stati-

Table III. The results of treatment in a group of 31 patients with "mixed" mucinous breast carcinoma type, and selected populational and clinical characteristics

Population or clinical characteristics	No. of treated patients	Actuarial 10-year cancer free survival in %	p (log-rank test)
* age:			
under 50	14	30.0	
51-60	3	0.0	
over 60	14	53.3	0.0002
* menopausal status:			
premenopausal	11	18.2	
menopausal and postmenopausal	20	47.2	0.0107
Localisation of tumour in the breast:			
Outer quadrants	22	24.6	
Other parts of the breast	9	44.4	0.8181
*clinical nodal status (N):			
N0	14	62.9	
N1	14	25.7	
N2	3	33.3	0.1056
*tumour grading acc. To TNM:			
I°+ II°A	15	64.0	
II°B	9	22.2	
III°	7	17.9	0.1472
Size of mass in the breast assessed by a pathologist in operation material (pT):			
Up to 4 cm	21	50.3	
Over 4 cm	10	25.0	0.1695
* microscopic nodal status (pN):			
pN0	14	71.4	
pN+(1-3)	5	0.0	
pN+(>3)	12	19.7	0.5711
Total	50	38.7	

* statistically significant differences, log-rank test, $p<0.05$

stically significant chance of 10-year cancer-free survival was observed in patients over 60 years of age, menopausal or postmenopausal.

The treatment results by MIB-1 index, *p53* and *c--erb B2* expression, and the presence of hormonal receptors in a group of patients with mixed mucinous breast carcinoma type are presented in Table IV.

Table IV does not show any of the immunohistochemically evaluated factors to have statistically significant effect on cancer free survival.

Table V presents treatment results in a studied group of 81 patients with mucinous carcinoma of the breast, by type of surgery.

The disparity between survival of patients treated with Patey or Halstead methods should be explained by different clinical composition of the compared groups; 84% of patients operated by Halstead method had stage III disease.

Reviewing the data shown in Table VI it should be noted that in the entire studied group, statistically significant, unfavourable influence on 10-year symptom--free survival in the multivariate Cox model was observed in patients with mixed mucinous breast carcinoma type, under 60 years of age, and clinically axillary positive.

Table VII shows that in the group of patients with pure mucinous breast carcinoma type only positive axilla-

Table IV. The results of treatment of "mixed type" of 31 patients and immunohistochemical evaluations

Discriminants	No. of treated patients	Actuarial 10-year cancer free survival in %	p (log-rank-test)
MIB-1 index			
≤ 14	12	50.0	
>14	19	31.6	0.2784
* *p53* gene expression			
yes	4	25.0	
no	27	65.8	0.1442
c-erb B2 gene expression:			
yes	4	37.5	
no	27	35.6	0.5922
Oestrogen receptor:			
present	25	34.5	
absent	6	31.3	0.7857
Progesterone receptor:			
present	17	32.4	
absent	14	55.6	0.5494

Table V. The results of treatment and the type of surgery

Type of surgery	No. of treated patients	Actuarial 10-year cancer free survival in %
Halsted surgery	25	40.0
Patey surgery	54	69.6
Tumorectomy (followed by irradiation)	2	100.0
Total	81	60.5

Table VI. The results of a multivariate analysis of prognostic factor in whole group of 81 patients

Variable	Variant	Relative risk	Significance p for relative risk
microscopic mucinous type	Pure	1.00	-
	Mixed	4.50	0.0013
age of patients	≤60	4.42	0.0013
	>60	1.00	-
clinical axillary status	N0	1.00	-
	N1	3.60	0.0151
	N2	25.86	0.0000

Table VII. The results of multivariate analysis of prognostic factors in a group of 50 patients with "pure" mucinous carcinoma of the breast

Variable	Variant	Relative risk	Significance p for relative risk
Clinical axillary status	N0	1.00	
	N1	5.47	0.0670
	N2	23.18	0.0038

Table VIII. The results of a multivariate analysis of prognostic factors in a group of 31 patients with "mixed" mucinous carcinoma of the breast

Variable	Variant	Relative risk	Significance p for relative risk
Age of patients	≤60	6.76	
	>60	1.00	0.0161

ry metastases in N2 advanced level have a statistically significant, unfavourable effect on 10-year cancer-free survival in a multivariate Cox model.

Table VIII shows, that in a group of patients with mixed mucinous breast carcinoma type, only the patients age – below 60 had astatistically significant, unfavourable effect on 10-year cancer-free survival in a multivariate Cox model.

Reviewing the data presented in Tables VI, VII, VIII it can be stated that the independent prognostic factors are:

- in the entire group of patients with mucinous carcinoma of the breast: microscopic type, patient` s age and clinical axillary status,
- in the group of patients with pure type of mucinous carcinoma of the breast: clinical axillary status,
- in the group with mixed mucinous breast carcinoma type: patient` s age.

Causes of treatment failure

By the time this study was completed, therapy was unsuccessful in 28 patients of the entire assessed group. Patients' follow-ups and causes of treatment failure are presented in Table IX.

Discussion

Analysis of the clinical material has been made, covering 81 women with mucinous carcinoma of the breast who had received initial surgical treatment at the Oncology Centre, Cracow Branch, in the years 1952-1993. This analysis served as a basis for achieving the objectives of the present study.

Populational and clinical features of mucinous al carcinoma of the breast

The characteristic populational and clinical features of mucinous carcinoma of the breast found in the studied group of patients, are as follows:

- mean age – 62 years (30-84),
- patients being menopausal or postmenopausal,
- mean time of symptoms duration -8 months (1-36),
- most common localisation in the outer quadrant of the breast (59.3%),
- in over 70% of patients the lump in the breast (pT) not larger than 4 cm,
- in over 60% of patients, microscopically negative axillary nodes.

In the literature, the mean age of patients with mucinous carcinoma of the breast ranges from 50 to 68 years [5, 9, 22, 43] however, a majority of authors stress that it usually exceeds 60 years [1]; acc. to Clayton [22] it is 63 years, acc. to Fentiman [9] – 62 years. All authors agree that patients with mucinous carcinoma of the breast are older than patients with ductal infiltrating malignancy [1, 22].

The literature also confirms the author`s observations that most mucinous carcinoma patients are either menopausal or postmenopausal [1, 9, 22]; in the material studied by Fentiman et al. [9] such patients constituted 82%, by Andre et al. [1] – 83.6%, and by Clayton [22] – 89%. Such clinical features of mucinous carcinoma of the breast found in the studied group of patients as: time of symptoms duration, most common localisation of tumour in the outer quadrants, and a high percentage of low advancement cases are fully supported by reports given literature [1, 9, 21, 22, 43].

Within the studied group, in over 70% of patients, the lump in the breast (pT) was not bigger than 4 cm, while its mean size was 3.6 cm. In the material investigated by Clayton [22) the mean size of lump in the breast was 3.2 cm; by Brennan [5] – 3.8 cm, by Fentiman et al. [9] – 3 cm, by Andre et al. [1] – 3.7 cm. In the material of Komaki et al. in 53.6% of patients the lump in the breast was smaller than 02 cm, and in 37.8% it ranged from 2 to 5 cm.

Over 60% of patients in the described group had no microscopically detected axillary metastases; Brennan`s material [5] comprised 68% of such patients, Andre et al.`s [1] – 68.3%.

Table IX. Follow-up and causes of treatment failure in 28 patients from the studied group

Follow-up and causes of treatment failure	No of patients	
	No	%
distant mucinous metastases	17	60.7
distant mucinous metastases + loco-regional recurrence	5	17.9
loco-regional mucinous recurrence	2	7.1
tumour of the opposite breast (ductal infiltrating)	1	3.6
other causes	3	10.7
Total	28	100.0

In the studied group of patients, definite differences were found between the clinical outcomes of pure and mixed types of mucinous breast carcinoma:

- patients with pure type were statistically significantly older than patients with mixed type (68% of patients over 60 years of age compared to 45%). This observation is confirmed by other reports [1, 20, 33],
- the percentage of premenopausal women was nearly double in the group of patients with mixed type (35.5% as compared to 18%),
- the percentage of patients with the lump in the breast exceeding 4 cm was higher in the group of patients with mixed type of mucinous carcinoma of the breast (32.3% vs. 28%). A majority of authors stress that in patients with mixed mucinous type, the lumps in the breasts are usually considerably bigger than in patients with pure mucinous type [9]; in the material studied by Toikkanen and Kujari (153) the percentage of lumps over 5 cm in size was 22% in the pure type group, and 48% in the mixed type group. In Brennan`s material, the mean lump size was 1.96 cm in pure and 2.62 cm in mixed type [5], in Fentiman et al.`s material [9] – 2.2 cm and 3.2 cm. Only a few authors did not find any differences in this respect [1],
- in the studied group of patients with mixed type of mucinous carcinoma of the breast, axillary metastases were statistically more common on microscopic examination (pN+= 54.8% vs. 30%). This phenomenon is confirmed by numerous data from literature [2]; in the material studied by Rasmussen axillary metastases were found in 3% patients with pure and in 33% of patients with mixed type of mucinous carcinoma of the breast; by Komaki et al. respectively 15% and 46%, Scopsi et al. – 29% and 65%, Andre et al. [1] – 26% and 41%, Fentiman et al. [9] – 14% and 46%. Generally, in the literature, axillary metastases are found in 3-29% of patients with pure, and in 33-86% of patients with mixed carcinoma of the breast [1, 8, 9, 20].

Summing up the results of own studies and the data from literature, it should be concluded that mucinous carcinoma of the breast, and particularly its pure form, present specific population and clinical characteristics: a more advanced age of patients and relatively slow growth – with long time of symptoms duration, low percentage of large lumps in the breast and metastases to axillary nodes. The clinical outcome in mixed type of mucinous carcinoma is similar to the clinical outcome in ductal infiltrating carcinoma.

Features of mucinous carcinoma of the breast, determined by immunohistochemical evaluation

Immunohistochemical evaluation performed in the discussed group of patients revealed the following characteristic features of mucinous breast carcinoma:

- low MIB-1 index which, in over a half of the patients, does not exceed 14,
- low percentage of tumours presenting *p53* and *c-erb B2* expression – 12.3% and 9.9% respectively,
- over 90% of patients being oestrogen receptor positive and over 60% – progesterone receptor positive.

In the available literature I have not found any reports analysing the role of MIB-1 index selectively for mucinous breast carcinoma patients. There are reports discussing this problem in reference to the whole group of patients with mammary cancers [40, 41, 44]. Meyer et al., studying another index of neoplastic cell proliferation, i.e. the fraction of cells in the S-phase, concluded that in mucinous breast carcinoma it was low. Furthermore, literature does not provide reports offering selective evaluation of p53 and c-erb B2 expression in mucinous carcinoma of the breast, while there are obviously numerous reports discussing this problem in reference to the whole group of mammary cancer patients [39, 40, 45, 46].

The data from literature support my observation that a majority of mucinous breast carcinoma patients are hormone receptor positive [2, 47].

The investigated material was also used to compare the immunohistochemical evaluation in two groups of patients: those with pure and those with mixed type mucinous breast carcinoma. The comparison revealed the following statistically significant findings in the mixed type group:

- more patients with MIB-1 index over 14 (61.3% vs. 38%),
- fewer oestrogen receptor positive patients (80.6% vs. 98%).

No cytofluorometric evaluation was performed in the studied group; literature provides numerous data in this respect which does not raise any serious reservations. It is generally assumed that only a small percentage of mucinous breast carcinomas, particularly their pure type, is aneuploid (2). It has been pointed out that aneuploid tumours occur mainly in mixed type mucinous carcinoma patients and that aneuploidy positively correlates with axillary metastases and absence of oestrogen receptor (2).

Determining prognostic factors

Univariate analysis of prognostic factors revealed that significantly unfavourable influence on 10-year cancer-free survival in the entire group of patients, was exerted by: patients` age below 60, premenopausal status, clinically metastatic axillary nodes, stages IIB and III acc. to TNM, lump size in the breast (pT) over 4 cm, microscopically positive axillary nodes, mixed type of mucinous carcinoma of the breast and the presence of p 53 expression.

A multivariate analysis of prognostic factors using the Cox method showed that in the total group of patients studied, independent unfavourable prognostic factors were: mixed type of mucinous carcinoma, age below 60 and clinically positive axillary nodes. In the pure type group, the sole prognostic factor was clinical axillary status and in the mixed type group – age.

According to the data obtained from literature, the basic prognostic factor in patients with mucinous carcinoma of the breast is the microscopic status of axillary nodes [1, 22, 32]. In the presented group of patients, quite unexpectedly, but without doubt, this basic prognostic factor turned out to be not the microscopic but the clinical status of axillary nodes; even clinical stage N1 meant poorer prognosis.

The second prognostic factor generally approved in literature formucinous breast carcinoma patients is the microscopic type of tumour. Similarly as in the presented study, the mixed type is considered to be worse prognosing than the pure type [1, 4, 10, 24, 25]. Age being a prognostic factor, revealed in the studied group, finds support only in the conclusions reached by Avisar et al. [2] who advocate higher frequence of positive axillary metastases in young patients with mucinous breast carcinoma.

Some authors suggest the lump size in the breast to be a prognostic factor, with 5 cm treated as a cut-off value [1, 22]. In the studied material, similarly as in the material investigated by Avisar et al. [2], this was not a significant prognosticator. Some authors stipulate the existence of other potential prognostic factors in patients with mucinous carcinoma of the breast, e.g. differentiation and cellularity level of the tumour, amount of mucin, argyrophylic level, presence of DCIS, neuroendocrine markers (NSE, SYN) etc. [1, 9, 20, 22, 23, 48].

Evaluation of the effectiveness in the treatment of patients with mucinous carcinoma of the breast

The studies performed have found initial operational therapy to be an effective procedure in patients with mucinous breast carcinoma. In the assessed group, the actuarial 10-year survival was 0.60, for pure mucinous type patients – 0.74, while for mixed type patients – 0.39. In the literature, cancer free 5-year survival in the mucinous breast carcinoma group ranges from 68% to 100% [5, 30-32, 47] and 10-year survival, from 55% to 77% [1, 5, 22, 47], mainly in relation to the ratio of pure to mixed type in the clinical material studied.

A majority of authors report that survival of mucinous breast carcinoma patients is longer than that obtained in the group of patients with the most common microscopical type of breast tumour – the ductal infiltrating carcinoma [9, 22]; this is true, in particular, for the pure mucinous type [1, 2, 9, 21].

According to a great many authors, the mixed type of mucinous carcinoma of the breast is related to a significantly worse prognosis than the pure type, and can be compared, in this respect, to the ductal infiltrating carcinoma [1, 4, 10, 24, 25]. Toikkanen and Kujari obtained 79% of cancer free 10-year survival in pure mucinous type group, 41% in mixed group, and 41% in the ductal infiltrating carcinoma patients. In the group presented by Andre et al. [1], 10-year disease free survival was observed in 74.8% of pure mucinous type patients and 20.3% of mixed type patients; in the group of Fentiman et al. [9] these values were 87% and 54% respectively. 15-year survival in the group described by Toikkanen and Kujari amounted to 85% in the pure and 63% in the mixed group, while 20- year survival presented by Scopsi et al. was 70% and 38% respectively, with 46% for ductal infiltrating carcinoma group.

Concluding, literature presents 10-year survival in the mixed mucinous breast carcinoma type as 20-66%, and in the pure type as 75 – 100% [1, 9, 24]. Considering that the mixed type comprises the ductal infiltrating component while the pure type does not, it should not be surprising that both the clinical outcome and prognosis bring the mixed type close to the ductal infiltrating type.

Opinions suggesting that mixed mucinous breast carcinoma has the same prognostic features and does not differ clinically from the pure type [2] are extremely rare in literature.

Determining optimum therapy for patients with mucinous carcinoma of the breast

In the past decades, women with mucinous carcinoma of the breast were initially treated with radical mastectomy; only few authors decided on simple mastectomy when treating older and node negative patients. The reports of Wasserman et al., Ucla et. al. and of Kurtz et al. from the eighties, showed that routine radical mastectomy in mucinous breast carcinoma patients was not justified; at present, mucinous breast carcinoma patients are generally treated with breast conservation therapy (lumpectomy plus irradiation) [2]. It is now obvious that patients with mixed type of mucinous breast carcinoma should receive the same therapy as patients with ductal infiltrating carcinoma at the corresponding stage, both in respect of local therapy and postoperative irradiation, chemo- and hormonotherapy. This conclusion is supported by own observations (only 38.7% of patients were cured) as well as numerous other reports [10, 22, 25].

Patients with pure mucinous carcinoma of the breast and negative axillary nodes are generally assumed to have very good prognosis (over 90% complete recoveries were obtained) and they do not require any adjuvant therapy [1, 4, 9, 21, 24, 30-32]. In own material, out of 35 women with pure type and negative axillary nodes who did not receive adjuvant therapy only two patients (5.5%) died of mucinous breast carcinoma. All 15 patients in this group with lump size in the breast (pT) not exceeding 2 cm and with no axillary node involvement, survived 10 years without cancer.

Recently it has even been suggested that if the tumour size in the breast of a patient with pure type of mucinous breast carcinoma does not exceed 2 cm, the therapeutic procedure may be limited to the excision of the lump with healthy tissue margin [9]. This opinion might be somewhat far-reached, but it is evident that the treatment of choice in patients with pure type of mucinous carcino-

ma of the breast would be breast conservation surgery, i.e. lumpectomy with axillary lymphadenectomy, followed by irradiation. In case of lumps not larger than 2 cm and absence of clinical features of axillary involvement, some authors suggest not to excise the axillary nodes [1, 2, 9], although there are many who oppose this opinion [22].

Own studies (only slightly over 40% of cured patients), as well as numerous reports by other authors, show that women with pure type of mucinous breast carcinoma and positive axillary nodes should receive the same therapy as patients with mixed type (and, in result, the same as patients with ductal infiltrating carcinoma at the corresponding stage). It is obviously recommended, in accordance with the current general guidelines, to apply breast conservation therapy with subsequent chemo- and/or hormonotherapy [1, 9, 20].

The basic cause of treatment failure in the studied group was the development of distant metastases, which is in accord with the data from literature [1, 2, 9, 20]. Some authors report cerebral infarction caused by mucin embolism that occurred in patients with mucinous carcinoma of the breast [49]. Further two patients were lost due to cerebral embolisms of unknown etiology.

Many authors describe late recurrence of mucinous breast carcinoma, 10 years or more after surgery [8, 22, 50]. In Gerschickter`s group, 14 of 59 patients had mucinous breast carcinoma recurrence within 6 to 18 years from diagnosis. In the material of Rosen and Wang, 42% of recurrences were found 12 years after therapy. In patients studied by Donegan and Spratt, out of 15 patients who died of mucinous breast carcinoma, 6 died between 10 to 20 years after operation. Clayton demonstrated that the mean survival of patients who died of mucinous carcinoma of the breast was 11 years [22]. The latest recurrences of the malignancy were described by Lee and Terry – 25 years, and by Sharnhorst and Huntrakoon – 30 years after diagnosis. In such situation, some authors stress the need of long-term observation of patients with mucinous breast carcinoma (15-20 years), which is often impossible due to the advanced age of majority of patients at the time of diagnosis [22]. In the studied group, observed from 5 to 46 years, no late recurrences were noted; similar absence of late recurrences was shown by Komaki et al., Toikkanen and Kujari, Fentiman et al., Wulsin and Schreiber, Rosen et al. [9].

Conclusions

1. The specific population and clinical features of mucinous breast carcinoma found in the evaluated group of patients are:
   – mean age – 62 years (30-84),
   – over 3/4 of patients being menopausal or postmenopausal,
   – mean time of symptoms duration – 8 months (1-36),
   – most common localisation of tumour in the outer quadrants of the breast,
   – in over 70% of patients, the lump size in the breast (pT) not exceeding 4 cm,
   – in over 60% of patients, microscopically negative axillary nodes.
2. The specific features of mucinous carcinoma of the breast found on immunuhistochemical evaluations are:
   – relatively low MIB-1 index which, in over a half of the patients, does not exceed 14 (2-46),
   – over 90% of patients being oestrogen receptor positive and over 60% – progesterone receptor positive,
   – low percentage of tumours presenting p53 and c-erb B2 expression – 12.3% and 9.9% respectively.
3. Independent unfavourable prognostic factors in patients with mucinous carcinoma of the breast are: patient`s age below 60, clinically positive axillary nodes and mixed tumour type.
4. Surgical treatment allows to obtain over 60% of 10-year cancer free survival in patients with mucinous carcinoma of the breast, of which 74% in the pure, and 39% in the mixed mucinous type group. The basic cause of treatment failure is generalisation of the malignant process.
5. All patients with mixed mucinous breast carcinoma type and those patients with pure mucinous type who are axillary positive, should receive the same treatment as patients with ductal infiltrating carcinoma at the corresponding stage of clinical advancement, both local and adjuvant.
6. For patients with pure mucinous type and negative axillary nodes, breast conservation therapy should be the main option, and it may be considered not to apply adjuvant systemic therapy.

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References

1. Andre S, Cunha F, Bernardo M. et al. Mucinous carcinoma of the breast: a pathologic study of 82 cases. *J Surg Oncol* 1995; 58: 162-165.
2. Avisar E, Khan MA, Axelrod D et al. Pure mucinous carcinoma of the breast: a clinicopathologic correlation study. *Ann Surg Oncol* 1998; 5: 447-450.
3. Beahrs OH, Shapiro S, Smart C et al. Report of the working group to review the National Cancer Institute – American Cancer Society Breast Cancer Detection Demonstration Projects. *J N C I* 1979; 62: 640-642.
4. Bland KI, Copeland EM. *The breast*. Philadelphia: WB Saunders Comp; 1998, 287.
5. Brennan MJ. Breast cancer. In: Holland JF, Frei E (eds.). *Cancer Medicin*. Philadelphia: Lea and Febiger; 1974.
6. Capella C, Eusebi V, Mann B et al. Endocrine differentiation in mucoid carcinoma of the breast. *Histopathology* 1980; 4: 1613-1615.
7. Chinyama CN, Davies JD. Mammary mucinous lesions: congeners, prevalence and important pathological associations. *Histopathology* 1996; 29: 533-536.
8. Donegan WL, Spratt JS. Cancer of the breast. Philadelphia: WB Saunders Comp; 1995, 243.

9. Fentiman IS, Millis RR, Smith P et al. Muccoid breast carcinomas: histology and prognosis. *Br J Cancer* 1997; 75: 1061-1062.
10. Fisher ER, Gregorio RM, Fisher B et al. The pathology of invasive breast cancer. *Cancer* 1975; 36: 1-5.
11. Fu YS, Maksem JA, Hubay CA et al. The relationship of breast cancer morphology and estrogen receptor protein status. In: Fenoglio CM, Wolff M (eds.). *Progress in surgical pathology*. New York: NY. Masson; 1981, 65.
12. Henderson IC, Harris JR, Kinne DW et al. Cancer of the breast. In: De Vita T, Hellman S, Rosenberg SA (eds.). *Cancer Principles and Practice of Oncology*. Philadelphia: Lippincott-Raven; 1997, 1197.
13. Hutter RVP. The influence of pathologic factors on breast cancer management. *Cancer* 1980; 46: 961-963.
14. Komaki K, Sakamoto KG, Sugano H et al. Mucinous carcinoma of the breast in Japan. A prognostic analysis based on morphological features. *Cancer* 1988; 61: 989-991.
15. Melamed MR, Robbins GF, Foote FW. Prognostic significance of gelatinous mammary carcinoma. *Cancer* 1961; 14: 699-702.
16. Nemoto T, Vana J, Bedwain RN et al. Management and survival of female breast cancer: results of a national survey by the American College of Surgeons. *Cancer* 1980; 45: 2917-2919.
17. Norris HJ, Taylor HB. Prognosis of mucinous (gelatinous) carcinoma of the breast. *Cancer* 1965; 18: 879-881.
18. Adeyinka A, Mertens F, Idvall I et al. Cytogenetic findings in invasive breast carcinomas with prognostically favourable histology: a less complex karyotipic pattern? *Int J Cancer* 1998; 79: 361-365.
19. Allen C, Cox EB, Manton KG et al. Breast cancer in the elderly. Current patterns of care. *J Am Geriatr Soc* 1986; 34: 637-640.
20. Fentiman IS. *Detection and treatment of breast cancer*. London: Martin Dunitz; 1998, 283.
21. Berg JW, Hutter RVP. Breast cancer. *Cancer* 1995; 75: 257-260.
22. Clayton F. Pure mucinous carcinomas of breast: morphologic features and prognostic correlates. *Hum Pathol* 1986; 17: 34-36.
23. Coady AT, Shousha S, Dawson PM et al. Mucinous carcinoma of the breast: further characterization of its three sybtypes. *Histopathology* 1989; 15: 617-620.
24. Ermilova VD, Knylova MO. Slizistyi rak molochnoi zhelezy (kliniko--morphologicheskaia kharakteristika). *Arkh Patol* 1989; 51: 38-41.
25. Fisher ER, Anderson S, Redmond C et al. Pathologic findings from the National Surgical Adjuvant Breast project protocol B-06. *Cancer* 1993; 71: 2507-2510.
26. Aghadiuno PU. Cancer of the male breast: analysis of forty – three cases in Ibadan, Nigeria. *Afr J Med Sci* 1987; 16: 15-18.
27. Dixon JM, Page DL, Elton RA et al. Long-term survivors after breast cancer. *Br J Surg* 1985; 72: 445-450.
28. Elledge RM, Mc Guire WL, Osborne CK. Prognostic factors in breast ancer. *Semin Oncol* 1992; 19: 244-247.
29. Fowble B, Goodman RL, Glick JH, Rosato EF. *Breast cancer treatment*. St. Louis: Mosby Year Book Inc; 1991, 178.
30. Cutler S J, Black MM, Mork T et al. Further observations on prognostic factors in cancer of the female breast. *Cancer* 1969; 24: 653-655.
31. Fisher ER, Palekar AS, Redmond C et al. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol no. 4). VI. Invasive papillary cancer. *Amer J Clin Pathol* 1980; 73: 313-315.
32. Fisher ER, Redmond C, Fisher B, Bass G. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Projects (NSABP) prognostic discriminants for 8 year survival for node – negative invasive breast cancer patients. *Cancer* 1990; 65: 2121-2124.
33. Anderson TJ, Lamb J, Donnan P et al. Comparative pathology of breast in a randomized trial of screening. *Br J Cancer* 1991; 64: 108-111.
34. Dawson AE, Mulford DK. Fine needle aspiration of mucinous (colloid) breast carcinoma. Nuclear grading and mammographic and cytologic findings. *Acvta Cytol* 1998; 42: 668-670.
35. Duane GB, Kanter MH, Branigan T et al. A morphologic and morphometric study of cells from colloid carcinoma of the breast obtained by fine needle aspiration. Distinction from other breast lessions. *Acta Cytol* 1987; 31: 742-745.
36. Cardenosa G, Doudna C, Eklund G. Mucinous (colloid) breast cancer: clinical and mammographic findings in 10 patients. *A J R* 1994; 162: 1077.
37. Chopra S, Evans AJ, Pinder SE et al. Pure mucinous breast cancer – mammographic and ultrasound findings. *Clin Radiol* 1996; 51: 421-425.
38. Fischer U, Kopka L, Grabbe E. Invasive mucinous carcinoma of the breast missed by contrast-enhancing MR imaging of the breast. *Eur Radiol* 1996; 6: 929-932.
39. Domagała W, Striker G, Szadowska A. et al. P53 protein and vimentin in invasive ductal NOS breast carcinoma relationship with survival and sites of metastases. *Eur J Cancer* 1994; 30: 1527-1530.
40. Domagała W. Klasyczne i nowe czynniki prognostyczne i predykcyjne w raku sutka u kobiet. *Nowotwory* 1996; 46: 669-671.
41. Domagała W, Markiewski M, Harezga B et al. Prognostic significance of tumor cell proliferation rate as determined by the MIB-1 antibody in breast carcinoma: its relationship with vimentin and p53 protein. *Clin Cancer Res* 1996; 2: 147-150.
42. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc B* 1972; 34: 187-189.
43. Bastidas B, Panduro S, Baron JG et al. Carcinoma mucinoso de mama. Analisis de 12 casos. *Ginecol Obstet Mex* 1989; 57: 64-66.
44. Ellias PA, Makris A, Burton SA et al. Comparision of MIB-1 proliferation index with S-phase fraction in human breast carcinomas. *Br J Cancer* 1996; 73: 640-641.
45. Barbereschi M. Prognostic value of the immunohistochemical expression of p53 in breast carcinomas – a review of the literature involving over 9000 patients. *Applied Immunohistochemistry* 1996; 4: 106-110.
46. Domagała W, Harezga B, Szadowska A et al. Nuclear p53 protein accumulates preferentially in medullary and high-grade ductal but rarely in lobular breast carcinomas. *Am J Pathol* 1993; 142: 669-672.
47. Ariel JM. Results of treating 1178 patients with breast cancer by radical mastectomy and postoperative irradiation where metastases to axillary lymph nodes occured. *J Surg Oncol* 1989; 12: 137-141.
48. Cubilla AL, Woodruff JM, Erlandson RA. Comparative clinicopathologic study of endocrine-like and ordinary mucinous carcinomas of the breast. *Lab Invest* 1984; 50: 14A-16A.
49. Deck JHN, Lee MA. Mucin embolism to cerebral arteries: a fatal complications of carcinoma of breast. *Can J Neurol Sci* 1978; 5: 327-330.
50. Cheatle GL, Cutler M. Gelatinous carcinoma of the breast. *Arch Surg* 1930; 20: 568-570.

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