N. V. Kovtun,
DSc in Economics, Professor,
Department of Statistics and Demography,
Taras Shevchenko National University of Kyiv,
E-mail: kovtun_natali@ukr.net
Researcher ID: M-6596-2017,
ORCID: https://orcid.org/0000-0002-2935-8597;
I. M. Motuziuk,
PhD in Medicine, Associate Professor,
Department of oncology,
O. O. Bogomolets National Medical University,
E-mail: 180978igor@gmail.com
ORCID: https://orcid.org/0000-0002-8332-3280;
R. O. Ganzha,
Postgraduate Student,
Taras Shevchenko National University of Kyiv,
E-mail: ganzha.roman.alex@gmail.com
ORCID: https://orcid.org/0000-0002-3418-7593

A Statistical Modelling Approach for Guiding the Optimum Surgical Intervention of Breast Cancer. Part I

Breast cancer is most common tumour diagnosis for women worldwide. Over the last almost 40 years widespread adoption of mammographic screening has established Breast Conserving Surgery (BCS) followed by irradiation as the most practised treatment of choice. However, in absence of tools to determine the optimal quantum of tissue to be excised the debate continues for achieving a balance between the effectiveness of surgical intervention and the later stage personalisation of treatment, and so, a wide variation in practice is a common phenomenon globally. We attempt to introduce a definite measure that determines efficacy of BCS while protecting aesthetic value of life for Women affected with breast cancer.

74 mammography examinations and the surgical interventions of those women underwent for the management of breast cancer were used to compute the coefficient of lesion. In first step the lesion and the mammary gland proper are measured applying geometry. In the second step volume of tissue mass to be removed was calculated taking into account the measures from the 1st step and we present the coefficient of lesion mathematically. We empirically illustrated our methodological approach for determining the tissue mass to be excised.

Conventionally, it is assumed that if the volume of tissues to be removed does not exceed 25% of the volume of the mammary gland, a Breast Conserving Surgery, is performed, however, our empirical illustration demonstrated that the established decision making parameter is not tenable for determining the extent / type of surgery undertaken. We have developed a coefficient aligned with the stage of the carcinoma and founded the base for developing a statistical (mathematical) model. Application of such a model accommodating tumour biology and patient characteristics shall not only provide intraoperative real time information to surgeons but also predict the prognosis of optimal surgical intervention of breast cancer.

The next step is to develop a model using the data of the mammographic examination and the coefficient of breast lesion as covariates for determining the potentially effective volumes of surgical intervention needed, and plan reconstructive measures considering the effect of time on such intervention.

Key words: *coefficient of lesion for mammary gland, optimum surgical intervention, breast cancer, Breast Conserving Surgery, mastectomy, two-dimensional mammography.*

Background

Globally, breast cancer is the most frequently diagnosed cancer in women. Incidence rates vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe (WHO, 2017). There are about half a million deaths per year from breast cancer worldwide making it the most common cause of female cancer death in both the developed and developing world [1].

While substantial advances have been made in breast cancer research and treatment in the last decade, there remain significant gaps in translating this newly acquired knowledge into the survivorship experience. Surgery remains the primary choice of

treatment for most women, with breast conservation (plus whole breast radiotherapy) providing similar outcomes to mastectomy [2]. Clinical decision-making tools to support individualised treatment can influence treatment choices and experiences [3]. A significant number of patients are overtreated to achieve the improved overall survival in early breast cancer, since individual risk of disease recurrence and sensitivity to intervention remains elusive. A review study has found that excising a wider margin of tissue around an invasive malignant tumour does not result lower rates of local recurrence [4]. Morrow et al. have echoed similar views that available evidences do not support that wider cancer-free surgical margins reduce the risk of local recurrence after lumpectomy for invasive breast cancer [5].

Despite strong evidence supporting the use of Breast Conserving Surgery (BCS), the majority of women are continued to be treated with mastectomy [6]. With the widespread adoption of sentinel node biopsy (SNB) limiting surgery to the axilla has substantially reduced arm morbidity [7]. Swanson and Rynearson established that removal of additional tissue worsens the cosmetic result while finding of the positive margin is not necessarily a precise indicator of the quantum of disease left in the breast [8].

Adequacy of the excision margin is well acknowledged guide for the success of BCS [8]. The threshold that surgeon accepts as an adequate for surgical margin varies widely [9–11]. Diagnostic pathology does not find any consensus on this long standing and extensive debate and that results a considerable variations in clinical practice [12]. A detailed understanding of tumour is required to support decisions around surgical management and to define optimal treatment strategies for an individual patient.

Personalisation of treatment avoids radiation-induced toxicity in later stage [13]. Using a sample of 16,643 patients of stage 1 and stage II breast tumour treated, Morrow et al. (2001) demonstrated that the predictors of BCS often do not correspond to those suggested in case management protocol and guidelines [6]. Abandoning practice of conventional surgical margins or some other arbitrary width has the potential to dramatically decrease healthcare costs but also simultaneously to improve the cosmetic outcome of BCS [14].

The need for an objective and patient specific decision-making information is well documented [15; 16]. This paper presents a "theragnostic" tool [17], an approach, never explored earlier, that enables surgeons to determine an optimal extent of breast tissue excision.

Data and methods

Data for this study comes from retrospective review of 74 mammography reports. Mammographic screening has been shown to be effective in reducing the mortality from breast cancer [18–23]. Following the guidelines of American Joint Committee on Cancer, the stages of breast tumour classified were 6 in the sample that we used.

A two-dimensional mammography was performed on 74 women of different age groups and having different stages of breast cancer. The mammography captured breast tissue images on different planes (cross-sectional – Cranial and Caudal, and Sagittal). We assessed:

1. Tumour localization by quadrants (upper-outer, upper-inner, lower-outer, lower-inner, at the proximity of two quadrants and tumour in dispersed location all over the mammary gland).

2. Tumour shape (round, irregular, polymorphic).

3. Consistency of tumour (tubercular, hard, small-jagged, polycyclic).

4. Tumour contours (sharp, blunt).

5. Composition of tumour (homogeneous, heterogeneous).

6. Infiltrative growth presentation (local, slightly expressed, moderately expressed, severely expressed, absent).

7. Presence of edema.

8. Presence of nipple retraction.

9. Presence of "path" to the nipple.

10. Presence of tumour invasion to the large mammary (pectoralis major) muscle.

11. Mammographic density of the mammary gland (breast): nodular fibro adenomatosed, diffuse fibro adenomatosed, absent.

12. Coefficient of mammary gland (breast) lesion – size of tumour relative to mammary gland (breast) volume.

Above characteristics (attributes) were considered as the deciding factors for determining the size of affected mammary gland (breast) parenchyma to be removed during surgical intervention.

We calculated the coefficient of lesion from the data of mammographic examination as detailed here. For tumour:

Calculation of tissues mass to be removed: during mammography examination two imaginary lines were drawn – one connecting nipple-areolar region to pectoralis major muscle along the lateral and medial "visible" edge of the tumour (cranio-caudal projection – CC) and other, between upper and lower edge of the tumour (sagittal projection – S).

For mammary gland:

Calculation of volume followed three-dimensional measurements – CC, S and H where H is the "height" of mammary gland (breast tissue proper).

1st step: the volume of the mammary gland was computed using the ellipsoid formula divided by two yielding the volume of semi-ellipsoid:

$$V_{mg} = \frac{1}{2}\left[\frac{4}{3}\pi\left(\frac{CC}{2} \cdot \frac{S}{2} \cdot H\right)\right]. \qquad \text{(Eq. 1)}$$

2nd step: the volume of tissue mass to be removed was calculated from ellipsoid by two approaches:

a) using greater semi-axis: max {CC, S}. If CC>S, then

$$V_{Tum} = \frac{4}{3}\pi\left(\left(\frac{CC}{2}\right)^2 \cdot S\right); \qquad \text{(Eq. 2)}$$

if CC<S, then

$$V_{Tum} = \frac{4}{3}\pi\left(\left(\frac{S}{2}\right)^2 \cdot CC\right); \qquad \text{(Eq. 3)}$$

b) using smaller semi-axis: min {CC, S}. Both formulas (Eq. 2) and (Eq. 3) were used in our calculations.

The use of these two approaches is for reasons: if coefficient of the lesion computed using greater semi-axis (a) is bigger than 100%, and then it has to be re-derived using smaller semi-axis (b). In case both coefficients calculated according to approaches a) and b) give more than 100% of affliction with lesion, the coefficient of the lesion has to be set to cut-off value equal to 100%.

The coefficient of lesion for mammary gland is calculated as:

$$K_{lesion} = \frac{V_{Tum}}{V_{mg}} \cdot 100\%. \qquad \text{(Eq. 4)}$$

Empirical illustration

In order to assess the adequacy of the proposed approach the variance of coefficient of lesion was checked across different stages (Table 1). We found that the coefficient of lesion increased with the increase in the severity of the disease (stage) (p-value = 0.06) (Table 1, Figure 1, based on data from retrospective review of 74 mammography reports).

Table 1

Coefficient of lesion variance across stages of the disease

Stage of tumour	Number	Coefficient of lesion, %	Minimum value	Maximum value
1	15	1.71 (4.93)	0.00	11.53
2A	28	8.48 (3.60)	1.28	15.67
2B	20	12.23 (4.27)	3.72	20.74
3A	8	19.61 (6.74)	6.16	33.07
3B, 3C	3	33.04 (11.01)	11.07	55.01
Total	74	10.32 (2.30)	17.05	23.63

Notes:
- figures in parentheses indicate standard error;
- all values are significant at $p < 0.01$;
- minimum and maximum values are at confidence interval of 95%.
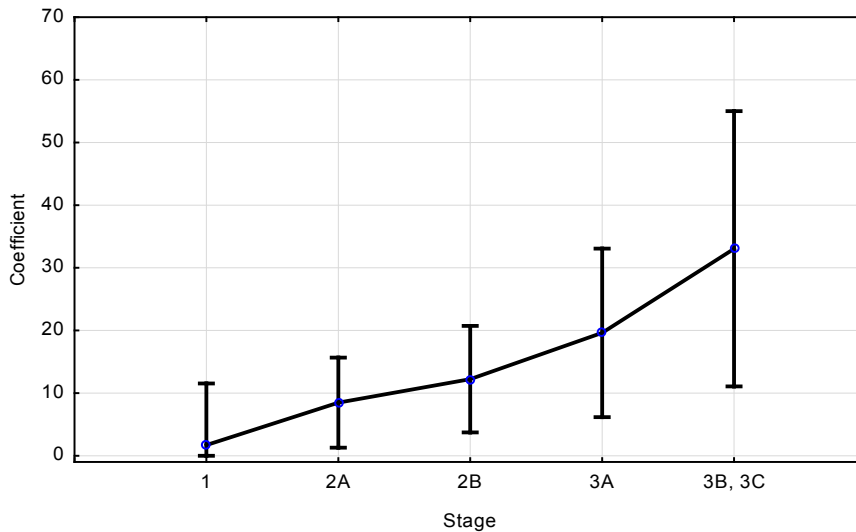

Figure 1. Average value of coefficient of lesion over stages of disease according to linear model

Table 2 presents the stage of the disease and the type of surgery. Test of independence was significant at p-value equal to 0.03. Therefore, with advancement of tumour stage, the chance for mastectomy increases as well. At the Stage 1 of the tumour, accounted for only 20% mastectomy of all types of surgeries, the share of Stage 2A was 57%, and Stages 2B and 2C, equal to 75%. The lower percentage (more than half) of mastectomy in Stage 3 (groups four and five) compared to the Stage 2 can be explained by relatively substantial a smaller number of observations in Stage 3.

Table 2

Dependency between type of surgery and the stage of the tumour

Stage of tumour	Quadrant BCS	Mastectomy	Total
1	12	3	15
2A	13	15	28
2B	5	15	20
3A	4	4	8
3B, 3C	1	2	3
Total	34	40	74

Conventionally, it is assumed that if the volume of tissues to be removed does not exceed 25% of the volume of the mammary gland, a BCS is performed, and if necessary, the correction of the form or size of the contralateral mammary gland breast is done to achieve symmetry. Alternately, if volume of the mammary gland tissue to be removed exceeds 25%, then a mastectomy is performed with a one-stage breast reconstruction by autologous or allograft materials upon patient's choice.

In our data, the decision border of 25% was not justified (p-value = 0.1226). The results of the test showed that the differences between groups in the coefficient of lesion are random (Table 3) translating the fact that the established decision-making parameter is not tenable for determining the extent / type of surgical intervention.

Further, we also examined possible effect of the tumour attributes on the decision of surgical intervention. Table 4 presents our findings on this dimension.

Table 3

Dependency between the type of surgery and the degree of lesion

Coefficient of lesion	Quadrant BCS	Mastectomy	Total
<25%	32	35	67
>25%	1	6	7
Total	33	41	74

Table 4

Results of testing the significance of the effects that determine the extent of surgical intervention

Tumour attributes	Test results (p-value)	
	Pearson Chi-square	Fisher exact, two-tailed
1. Stage of disease*	12.55 (0.01)	x
2. Tumour localization	8.04 (0.53)	x
3. Tumour form	1.81 (0.40)	x
4. Tumour contours	6.332 (0.28)	x
5. Tumour contours sharpness	3.491 (0.32)	x
6. Structure of tumour	0.04 (0.83)	(0.99)
7. Infiltrative growth expressiveness	9.908 (0.07)	x
8. Edema presence	2.45 (0.11)	(0.20)
9. Presence of nipple retraction *	8.210 (0.004)	(0.01)
10. Presence of "path" to the nipple*	10.55 (0.001)	(0.022)
11. Presence of symptoms of tumour invasion in the large mammary muscle	0.104 (0.94)	(0.93)
12. Mammographic density of the mammary gland	0.235 (0.89)	x

* p-value < 0.05.

Therefore, only two attributes are (except for the stage, Table 2), having the significant effect to determine the type of surgical intervention that was not at random:

a) nipple retraction (p-value = 0.004), Table 5.

The ODDS Ratio (OR) was being computes as follows:

$$OR = \frac{32 \cdot 16}{24 \cdot 2} = 10.7 .$$

It means the BCS was indicated with 10.7 times more often than mastectomy in the absence of nipple retraction.

b) "path" to the nipple (p-value = 0.001), Table 6.

Table 5

Dependence between type of surgery and absence of nipple retraction

Retraction of nipple	Quadrant BCS	Mastectomy	Total
0*	32	24	56
1*	2	16	18
Total	34	40	74

* 0 = absent; 1 = present.

Table 6

Dependence between type of surgery and presence/absence of "path" to the nipple

"Path" to the nipple	Quadrant BCS	Mastectomy	Total
0*	23	13	36
1*	11	27	38
Total	34	40	74

* 0 = absent; 1 = present.

Reciprocally, the presence of the "path" determined the need for mastectomy 4.3 times more often compared to another variant, ceteris paribas.

Discussion

The ongoing debate on the optimal treatment strategies and individual risk of recurrence of breast cancer demands an objective decision-making criterion. We have attempted to develop an approach that defines an optimal extent of surgical intervention with an effective cut-off for the surgical margin in BCS. We have used data from 74 mammography examinations and the surgical interventions of those women underwent for the management of breast cancer. We have developed a coefficient aligned with the stage of the carcinoma. Thus, our index can act as a tool to determine the extent of surgical excision and simultaneous choice of options for reconstructive surgery in the management of breast cancer. The confirmation of the tissue mass to be removed was subjected to the validation by the approach of worst-case scenario. Given Cranio-Caudal and Sagittal measurements, the tissue mass to be removed was maximized with Eq. 2 and Eq. 3 which in turn effectively penalized the model. Alternately, we have overcome the variability and instability in subset selection with a computationally efficient fashion establishing robustness in our approach. Our empirical illustration could not establish the rationale of conventional decision-making process where breast conserving surgery is performed when the volume of tissues removed from the breast does not exceed 25% of the gland tissue proper, and a mastectomy, when the volume of tissues removed from the breast exceeds 25% of the gland tissue proper.

Our findings and the techniques developed thus sets the foundation for developing a statistical model to realise the goal of an optimal balance between good cosmetic results and defining the optimal tissue excision. Such a model shall predict the intraoperative margin assessment and thus the prognosis of optimal surgical intervention of breast cancer. We shall integrate in our model biological knowledge of tumour and patient characteristics to accommodate risk factors. Application of statistical model in breast cancer management shall not only make surgical intervention more efficient and effective but also would ensure survival with enhanced quality of life and substantially reduced risk of recurrence for women with breast cancer.

To conclude, our approach shall bring the consensus on the contentious issue of margin status in BCS by defining the cut-off for the margin width. The next step is to develop a model using the data of the mammographic examination and the coefficient of breast lesion as covariates for determining the potentially effective volumes of surgical intervention needed, and plan reconstructive measures considering the effect of time on such intervention. Such an objective approach would not only improve the efficiency of breast cancer treatment, but also would ensure supposedly a better quality of life for patients after treatment. Arguably, such a model would contribute for reduction of the risk of recurrence and increase survival of women with breast cancer.

References

1. Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008. GLOBOCAN 2008. *International Journal of Cancer, 127,* 2893–2917.

2. Thompson, A. M., & Moulder-Thompson, S. L. (2012). Neoadjuvant treatment of breast cancer. *Annals of Oncology, 23,* x231–x236.

3. Lipkus, I. M., Peters, E., Kimmick, G., Liotcheva, V., & Marcom, P. (2010). Breast cancer patients' treatment expectations after exposure to the decision aid program adjuvant online: the influence of numeracy. *Medical Decision Making, 30,* 464–473.

4. Singletary, S. E. (2002). Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *The American Journal of Surgery, 184,* 383–393.

5. Morrow, M., Harris, J. R., & Schnitt, J. S. (2012). Surgical Margins in Lumpectomy for Breast Cancer – Bigger Is Not Better. *The New England Journal of Medicine, 367*(1), 79–82.

6. Morrow, M., White, J., Moughan, J., Owen, J., Pajack, T., Sylvester, J. et al. (2001). Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. *Journal of Clinical Oncology, 19(8),* 2254–2262.

7. Fleissig, A., Fallowfield, L. J., Langridge, C. I., Johnson, L., Newcombe, R. G., Dixon, J. M., et al. (2006). Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Research and Treatment, 95,* 279–293.

8. Gregory, E. E., Turnbull, A. K., Arthur, L. M., Thomas, J., Dodds, C., & Dixon, J. M. (2017). Margin width and local recurrence after breast conserving surgery for ductal carcinoma in situ. *European Journal of Surgical Oncology, 43,* 2029–2035.

9. Chiappa, C., Rovera, F., Corben, D. A., Fachinetti, A., Berardinis, V. D., Marchionini, V., et al. (2013). Surgical margins in breast conservation. *International Journal of Surgery, 11* (S1), S69–S72.

10. Dunst, J., & Dellas, K. (2011). Margins! Margins. Margins? How Important Is Margin Status in Breast-Preserving Therapy? *Breast Care, 6,* 359–362.

11. Azu, M., Abrahamse, P., Katz, S.J., Jagsi, R., & Morrow, M. (2010). What is an Adequate Margin for Breast-Conserving Surgery? Surgeon Attitudes and Correlates. *Annals of Surgical Oncology, 17 (2),* 558–563.

12. Blair, S.L., Thompson, K., Rococco, J., Malcarne, V., Beitsch, P.D., & Ollila, D.W. (2009). Attaining Negative Margins in Breast-Conservation Operations: Is There a Consensus among Breast Surgeons? *Journal of American College of Surgeons, 209 (5),* 608–613.

13. Coates, P. J., Appleyard, M. V., Murray, K., Ackland, C., Gardner, J., Brown, D. C., et al. (2010). Differential contextual responses of normal human breast epithelium to ionizing radiation in a mouse xenograft model. *Cancer Research, 70,* 9808–9815.

14. Vicini, F. A., Eberlein, T. J., Connolly, J. L., Recht, A., Abner A., Schnitt, S. J., et al. (1991). The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. *Annals of Surgery, 214,* 200-204.

15. Jacobs, L. (2008). Positive margins: the challenge continues for breast surgeons. *Annals of Surgical Oncology, 15,* 1271–1272.

16. Schwartz, G. F., Veronesi, U., Clough, K. B., Dixon, J. M., Fentiman, I. S., Heywang-Köbrunner S. H., et al. (2006). Consensus conference on breast conservation. *Journal of the American College of Surgeons, 203,* 198–207.

17. Pleijhuis, R. G., Graafland, M., Vries, J. D., Bart, J., Jong, J. S. D., & van Dam, G. M. (2009). Obtaining Adequate Surgical Margins in Breast-Conserving Therapy for Patients with Early-Stage Breast Cancer: Current Modalities and Future Directions. *Annals of Surgical Oncology, 16,* 2717–2730.

18. Tabar, L., Vitak, B., Chen, T. H.-H., Yen, A. M-F., Cohen, A., Tot, T., et al. (2011). Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology, 260(3),* 658–663.

19. Screening IUPoBC. (2012). The benefits and harms of breast cancer screening: an independent review. *Lancet, 380(9855),* 1778–1786.

20. Meeting, F. (1996). Breast-cancer screening with mammography in women aged 40–49 years. *International Journal of Cancer, 68(6),* 693–699.

21. Duffy, S., Tabar, L., Olsen, A., Vitak, B., Allgood, P., Chen, T. H.-H., et al. (2010). Cancer mortality in the 50–69 year age group before and after screening. *Journal of Medical Screening, 17(3),* 159–160.

22. Jensena, A., Ewertz, M., Cold, S., Storm, H., & Overgaard, J. (2003). Time trends and regional differences in registration, stage distribution, surgical management and survival of breast cancer in Denmark. *European Journal of Cancer, 39 (12),* 1783–1793.

23. Chen, T. H.-H., Jonsson, S. H, & Lenner, P. (2007). Effect of mammographic service screening on stage at presentation of breast cancers in Sweden. *Cancer, 109(11),* 2205–2212.

Н. В. Ковтун,
доктор економічних наук, професор,
кафедра статистики та демографії,
Київський національний університет імені Тараса Шевченка,
E-mail: kovtun_natali@ukr.net
Researcher ID: M-6596-2017,
ORCID: https://orcid.org/0000-0002-2935-8597;

І. М. Мотузюк,
кандидат медичних наук, доцент,
кафедра онкології,
Національний медичний університет імені О. О. Богомольця,
E-mail: 180978igor@gmail.com
ORCID: https://orcid.org/0000-0002-8332-3280;

Р. О. Ганжа,
аспірант,
Київський національний університет імені Тараса Шевченка,
E-mail: ganzha.roman.alex@gmail.com
ORCID: https://orcid.org/0000-0002-3418-7593

Статистичне моделювання для прогнозування обсягу операційного втручання при раку грудної залози

Підхід, розглянутий у роботі, орієнтований насамперед на те, щоб мати можливість на етапі діагностики визначитися з обсягами оперативного втручання. Це особливо важливо, коли розглядається захворювання жінок на рак грудної залози, оскільки мова йде не тільки про успішність боротьби з захворюванням і подоланням цього недугу, а й про збереження якості життя жінки після лікування. У цьому контексті успішність лікування слід розглядати з двох боків. З одного – це онкологічна ефективність самого лікування, а з іншого – якість життя, яка забезпечує це лікування в подальшому. Проведення онкопластичної або реконструктивної операції грудної залози забезпечує належну якість життя пацієнта. А різні обсяги оперативного втручання передбачають і різну підготовку до онкопластики та реконструкції залежно від того, яка буде виконана операція: мастектомія чи органозберігаюча операція.

У дослідженні за даними мамографії 74 пацієнтів і операцій, які їм були проведені, здійснено спробу визначитися з тим, які з мамографічних ознак є визначальними. Крім того, розроблений спеціальний коефіцієнт, який є кількісною характеристикою і узгоджений зі стадією захворювання, а отже, він є свого роду індикатором, що допоможе на етапі діагностики визначитися з обсягами операційного втручання, а відповідно, і з варіантами реконструкції. Традиційно вважається, що якщо обсяг тканин, які підлягають видаленню, не перевищує 25% від обсягу грудної залози, то проводиться хірургія зі збереженням залози, і навпаки, якщо перевищує 25%, тоді слід виконувати мастектомію. Проте нашими результатами було доведено, що цей критерій не є надійним для визначення типу операції. Отже, встановлення точного відсотка при плануванні обсягів оперативного втручання не є виправданим.

Розроблений коефіцієнт абсолютно узгоджений зі стадією захворювання. Крім того, створено базу для розроблення статистичної моделі, що враховує біологію пухлини і характеристики пацієнта. Застосування такої моделі не тільки забезпечує хірургів інформацією в реальному часі, а й уможливлює прогнозування обсягів оптимального хірургічного втручання при раку грудної залози.

Наступним кроком передбачається розробка моделі, яка надасть можливість, використовуючи дані мамографічного обстеження і значення коефіцієнта ураження грудної залози як коваріати, достатньо ефективно визначати потенційні обсяги оперативного втручання, завчасно планувати одномоментні реконструктивні заходи. Це дозволить не тільки підвищити онкологічну ефективність лікування хворих на рак грудної залози, а й забезпечить належну якість їх життя після проведення лікування, що, своєю чергою, знизить ризики виникнення рецидивів і підвищить виживаність жінок, хворих на рак грудної залози.

Ключові слова: *коефіцієнт ураження грудної залози, оптимальне хірургічне втручання, рак грудної залози, органозберігаюча операція, мастектомія, двовимірна мамографія.*