# Overall survival and disease control rates for operable invasive breast cancer in the era of conservative surgery; retrospective, institutional, and five-year follow-up data

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# OVERALL SURVIVAL AND DISEASE CONTROL RATES FOR OPERABLE INVASIVE BREAST CANCER IN THE ERA OF CONSERVATIVE SURGERY; RETROSPECTIVE, INSTITUTIONAL, AND FIVE-YEAR FOLLOW-UP DATA

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**Summary**

*Background:* Following breast cancer treatment recommendations, the conservative approach is accepted and highly respected in the Clinical Hospital Center (CHC) Rijeka. However, we have found that institutional follow-up data are lacking. This retrospective analysis aims to update institutional data on survival and disease control rates.

*Methods:* From 2011 till 2014, 915 breast cancer patients underwent surgery at CHC Rijeka, and 615 were included in this analysis. The Institutional Ethics Committee approved the analysis.

*Results:* All patients were female, and the average age was 59 years. In the 5-year postoperative period, local, regional, and distant recurrence-free survival rates and overall survival and disease-free survival were calculated. All rates negatively correlate with a higher T and N status and a higher stage of the disease. The analysis has also demonstrated that in the pT1-3 pN0-1 subgroup, sentinel lymph node biopsy (SLNB) was not inferior to axillary lymph node dissection (ALND) in terms of locoregional control of disease and overall survival.

*Conclusion:* Besides updating institutional data, the analysis confirmed that overall survival and locoregional control of the disease in the upfront-surgery patients are similar between pN0 and pN1 subpopulations and between pN2 and pN3, but statistically significantly different between pN0-1 and pN2-3. Currently ongoing, prospective observational multicenter clinical trial aims to translate the significance of these results into the neoadjuvant era.

KEYWORDS: *breast cancer, survival, recurrence*

## BACKGROUND

In the last few decades, there is a constant de-escalation in the surgical approach to breast cancer (BC) patients. In all current guidelines, a conservative surgical approach is strongly recom-

mended for all early-stage BC patients. Following NSABP B-06 trial results (1), lumpectomy with whole breast radiation therapy (WBRT) became a standard of care for all T1-T2 BC patients, and due to the results of NSABP B-04 (2) and B-32 (3) trials, axillary lymph node dissection (ALND) was replaced with the sentinel lymph node biopsy (SLNB) in clinically node-negative (cN0) patients. Moreover, after the results of ACOSOG Z011 (4) and AMAROS (5) trial, ALND is no longer justi-

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fied, even in the case of pathologically node-positive (pN+) patients, considering that conservative breast surgery was made, WBRT would be conducted, and that no more than two nodes were found to be involved with metastasis. However, for the high-risk pN+ patients, radiotherapy of the lymphatic drainage is highly recommended instead of ALND.

In Clinical Hospital Center (CHC), Rijeka, all mentioned recommendations are accepted into clinical practice and are highly respected in everyday work. However, in this era of conservative surgery, we have found that institutional and national follow-up data are lacking. Most of the results regarding survival and disease control currently come from randomized controlled trials, i.e., from the highly selected patients. The purpose of this retrospective analysis is to report our latest institutional updates on survival and disease control rates of unselected populations from the era of conservative surgical and adjuvant oncological approaches and to discuss the potential influence of these results translated into the present neoadjuvant era.

## PATIENTS AND METHODS

From 2011 till 2014, 915 female BC patients were surgically treated in CHC Rijeka. However, we excluded patients older than 80 years or with M1 status at the time of surgery, recurrent, bilateral, or in situ disease, patients diagnosed with other malignant conditions, and those without follow-up data in the postoperative period. Therefore, 615 patients remained for the analysis. All data used for this analysis were extracted from the integrated hospital informatics system of CHC Rijeka with the approval of the Ethics Committee of CHC Rijeka.

Besides several T4 status patients, all patients were submitted to primary surgical treatment followed with adjuvant oncological systemic and locoregional treatment conducted according to the institutional protocol, i.e., according to the NCCN and St. Gallen's consensus guidelines for that period. In 283 cases (46.02%), lumpectomy and SLNB were performed, in 127 (20.65%) lumpectomy and ALND, in 34 (5.53%) mastectomy and SLNB, in 164 (26.99%) radical mastectomy, and for four patients (0.65%) there was no data of surgical treatment type. Axillary surgery was guided by NSABP B-32 (3), ACOSOG Z010 (6), ACOSOG Z011 (4), and AMAROS (5) trial criteria.

Overall survival (OS) rate is defined as a rate of patients surviving in 5 postoperative years or the last recorded control date. Distant disease-free survival or progression-free survival (DDFS or PFS) rate is defined as a rate of patients without evidence of distant metastasis, i.e., M1 status in 5 postoperative years or at the date of the last recorded control. Local recurrence-free survival (LRFS) rate is defined as a rate of patients without evidence of disease in the already treated or contralateral breast or thoracic wall in the five postoperative years or at the date of the last recorded control. Regional recurrence-free survival (RRFS) rate is defined as a rate of patients without evidence of disease in the lymph nodes of unilateral or contralateral axilla, infraclavicular, supraclavicular, or internal mammary lymph nodes in 5 postoperative years or to the date of the last recorded control. Disease-free, i.e., progression-free survival (DFS) rate is defined as patients' rate without evidence of recurrence in 5 postoperative years or the date of the last recorded control. All rates are calculated by the method of Kaplan Meier. The results are analyzed using Statistica 13 software and interpreted at statistical significance p = 0.05. Clinical and pathological T, N, and stage of the disease are defined according to the 8th Edition of AJCC Cancer Staging Manual.

## RESULTS

All patients were female, a mean age of 59 years at the time of the surgery and in stage T1-4 N0-3 M0 at the diagnosis time. The mean follow-up time was 56.5 months (+/- 10.8 months, range from 4 to 60 months). Study population characteristics and outcomes are displayed in Table 1.

Overall local, regional, and distant recurrence rates and overall survival and disease-free survival rates in 5 postoperative years are calculated by Kaplan Meier's method and displayed in Figure 1.

Furthermore, all rates are calculated in correlation with immunophenotype, T and N status, stage of the disease, and surgical treatment type. The results of these correlations are displayed in Table 2.

Table 1.

*Study population characteristics and the outcomes in terms of overall survival (OS), distant (DRFS), local (LRFS), and regional recurrence-free survival (RRFS) in the five years postoperatively.*

| | | Patients | | OS/5y | | | DRFS/5y | | | LRFS/5y | | | RRFS/5y | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | Yes N(%) | No N(%) | No data N(%) | Yes N(%) | No N(%) | No data N(%) | Yes N(%) | No N(%) | No data N(%) | Yes N(%) | No N(%) | No data N(%) |
| **Immunophenotype** | Luminal A | 227 | 36.91 | 215 (94.71) | 5 (2.20) | 7 (3.08) | 211 (92.95) | 9 (3.96) | 7 (2.57) | 216 (95.15) | 3 (1.32) | 8 (3.52) | 214 (94.27) | 5 (2.20) | 8 (3.52) |
| | Luminal B | 207 | 33.66 | 185 (89.37) | 3 (1.45) | 19 (9.17) | 172 (83.09) | 5 (2.41) | 10 (4.83) | 184 (88.88) | 10 (4.83) | 13 (6.28) | 182 (87.92) | 8 (3.86) | 17 (8.21) |
| | Luminal B HER-2+ | 75 | 12.20 | 65 (86.66) | 5 (6.67) | 5 (6.67) | 64 (85.33) | 6 (8) | 5 (6.66) | 68 (90.66) | 2 (2.66) | 5 (6.67) | 67 (89.33) | 3 (4) | 5 (6.67) |
| | HER-2+ | 53 | 8.62 | 38 (71.69) | 8 (15.09) | 7 (13.21) | 36 (67.92) | 12 (22.64) | 5 (9.43) | 41 (77.36) | 7 (13.21) | 5 (9.43) | 42 (79.25) | 5 (9.43) | 6 (11.32) |
| | TNBC | 48 | 7.80 | 34 (70.83) | 1 (2.08) | 13 (27.08) | 33 (68.75) | 8 (16.67) | 7 (14.58) | 34 (70.83) | 8 (16.67) | 6 (12.5) | 36 (75) | 2 (4.17) | 10 (20.83) |
| | Unknown | 5 | 0.81 | 2 (40) | 3 (60) | 0 | 2 (40) | 1 (20) | 2 (40) | 3 (60) | 0 | 2 (40) | 3 (60) | 0 | 2 (40) |
| **pT status** | T1 | 350 | 56.91 | 330 (94.29) | 3 (0.86) | 17 (4.86) | 328 (93.71) | 12 (3.43) | 10 (2.86) | 329 (94) | 12 (3.43) | 9 (2.57) | 330 (94.29) | 8 (2.29) | 12 (3.43) |
| | T2 | 195 | 31.71 | 162 (83.08) | 13 (6.67) | 20 (10.26) | 148 (75.90) | 32 (16.41) | 15 (7.70) | 170 (87.18) | 8 (4.11) | 17 (8.72) | 165 (84.62) | 8 (4.10) | 22 (11.28) |
| | T3 | 25 | 4.07 | 21 (84) | 3 (12) | 1 (4) | 19 (76) | 4 (16) | 2 (8) | 20 (80) | 3 (12) | 2 (8) | 21 (84) | 1 (4) | 3 (12) |
| | T4 | 42 | 6.83 | 26 (61.91) | 3 (7.14) | 13 (30.95) | 23 (54.76) | 13 (30.95) | 6 (14.29) | 27 (64.29) | 7 (16.67) | 8 (19.05) | 28 (59.52) | 6 (14.29) | 8 (19.05) |
| | Unknown | 3 | 0.49 | 0 | 3 (100) | 0 | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) |
| **pN status** | N0 | 371 | 60.33 | 343 (92.45) | 7 (/1.89) | 21 (5.67) | 343 (92.45) | 14 (3.77) | 14 (3.77) | 343 (92.45) | 14 (3.77) | 14 (3.77) | 345 (92.99) | 8 (2.16) | 18 (4.85) |
| | N1 | 148 | 24.07 | 135 (91.22) | 3 (2.03) | 10 (6.76) | 124 (83.78) | 17 (11.49) | 7 (4.73) | 135 (91.22) | 5 (3.38) | 8 (5.41) | 135 (91.22) | 3 (2.02) | 10 (6.76) |
| | N2 | 58 | 9.43 | 38 (65.51) | 6 (10.34) | 14 (24.14) | 32 (55.17) | 21 (36.21) | 5 (8.62) | 41 (70.69) | 7 (12.07) | 10 (17.24) | 40 (68.97) | 7 (12.07) | 11 (18.97) |
| | N3 | 35 | 5.69 | 23 (65.71) | 6 (17.14) | 6 (17.14) | 19 (54.29) | 9 (25.71) | 7 (20) | 27 (77.14) | 4 (11.43) | 4 (11.43) | 24 (68.57) | 5 (14.29) | 6 (17.14) |
| | Unknown | 3 | 0.49 | 0 | 3 (100) | 0 | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) |
| **TNM Stage** | IA | 263 | 42.76 | 250 (95.06) | 2 (0.76) | 11 (4.18) | 250 (95.06) | 6 (0.23) | 7 (2.66) | 249 (94.68) | 6 (2.28) | 8 (3.04) | 249 (94.68) | 5 (1.90) | 9 (3.42) |
| | IB | 20 | 3.25 | 20 (100) | 0 | 0 | 20 (100) | 0 | 0 | 20 (20) | 0 | 0 | 20 (100) | 0 | 0 |
| | IIA | 144 | 23.41 | 129 (89.58) | 4 (2.78) | 11 (7.64) | 125 (86.81) | 11 (7.64) | 8 (5.56) | 128 (88.89) | 11 (7.64) | 5 (3.47) | 129 (89.58) | 5 (3.47) | 10 (6.94) |
| | IIB | 60 | 9.76 | 52 (86.67) | 3 (5) | 5 (8.33) | 46 (76.67) | 10 (16.67) | 4 (6.67) | 54 (90) | 5 (8.33) | 6 (10) | 53 (88.33) | 1 (1.17) | 6 (10) |
| | IIIA | 56 | 9.11 | 45 (80.36) | 3 (5.36) | 8 (41.29) | 40 (71.43) | 13 (23.21) | 3 (5.36) | 46 (82.14) | 3 (5.36) | 5 (8.93) | 47 (83.93) | 3 (5.36) | 6 (10.71) |
| | IIIB | 33 | 5.37 | 19 (57.58) | 5 (15.15) | 9 (27.27) | 18 (54.55) | 10 (30.30) | 5 (15.15) | 22 (66.67) | 5 (15.15) | 8 (24.24) | 22 (66.67) | 3 (9.09) | 8 (24.24) |
| | IIIC | 36 | 5.85 | 24 (66.67) | 5 (13.89) | 7 (19.44) | 19 (52.78) | 11 (30.56) | 6 (16.67) | 27 (75) | 5 (13.89) | 4 (11.11) | 24 (66.67) | 6 (16.67) | 6 (16.67) |
| | Unknown | 3 | 0.49 | 0 | 3 (100) | 0 | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) | 0 | 0 | 3 (100) |
| **Surgery** | BCS+SLNB | 284 | 46.18 | 269 (94.72) | 2 (0.70) | 13 (4.56) | 268 (94.37) | 8 (2.82) | 8 (2.82) | 265 (93.31) | 11 (3.88) | 8 (2.81) | 268 (94.37) | 6 (23.24) | 10 (3.52) |
| | BCS+ALND | 127 | 20.65 | 116 (91.34) | 4 (3.15) | 7 (5.51) | 111 (87.40) | 12 (9.45) | 4 (3.15) | 116 (91.34) | 8 (6.3) | 3 (2.36) | 118 (92.91) | 2 (1.57) | 7 (5.51) |
| | M+SLNB | 34 | 5.53 | 31 (91.18) | 1 (2.94) | 2 (5.88) | 31 (91.18) | 1 (2.94) | 2 (5.88) | 32 (94.12) | 0 | 2 (5.88) | 32 (94.12) | 0 | 2 (5.88) |
| | M+ALND | 166 | 26.99 | 122 (73.49) | 15 (9.04) | 29 (17.47) | 107 (64.46) | 40 (24.1) | 19 (11.45) | 132 (79.52) | 11 (6.63) | 23 (13.86) | 125 (75.30) | 15 (9.04) | 26 (15.66) |
| | Unknown | 4 | 0.65 | 1 (25) | 3 (75) | 0 | 1 (25) | 0 | 3 (75) | 1 (25) | 0 | 3 (75) | 1 (25) | 0 | 3 (75) |

*Table Legend: Immunophenotype is defined according to 2013 St. Gallen consensus [7], TNBC=Triple negative breast cancer, N=number, OS/5y=5 years overall survival, DRFS/5y= 5 years disease-free survival, LRFS/5y=5 years local recurrence-free survival, RRFS/5y=5 years regional recurrence-free survival, pathological T, N and stage of the disease are defined according to current TNM classification by 8th Edition AJCC Cancer Staging Manual, BCS=breast conserving surgery (lumpectomy), SLNB=sentinel lymph node biopsy, M=mastectomy and ALND=axillary lymph node dissection.*
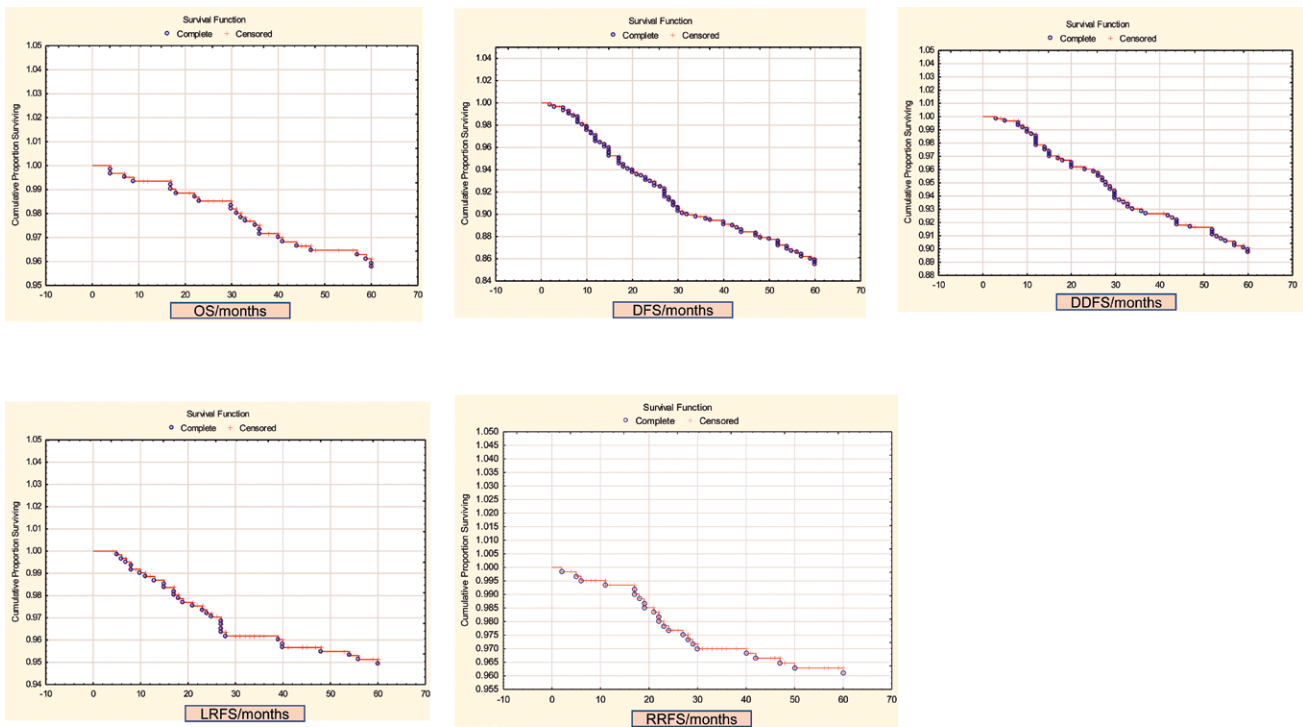
*Figure 1. 5 years overall survival rate (95.93%), disease-free survival rate (85.85%), distant disease-free survival rate (90.08%), local recurrence-free survival rate (95.12%), and regional recurrence-free survival rate (96.26%) for the whole cohort, calculated by the method of Kaplan Meier*

*Table 2.*
*Correlation of survival rates with immunophenotype, T, N, and stage of the disease are calculated, and the test results (Chi-square) with the associated p-values are displayed for each correlation.*

|  | Test statistic | OS | DFS | DDFS | LRFS | RRFS |
|---|---|---|---|---|---|---|
| Immunophenotype | Chi-square | 27.051 | 37.359 | 26.978 | 30.577 | 7.062 |
|  | p-value | 0.00002 | 0.00000 | 0.00003 | 0.00000 | 0.13260 |
| T status | Chi-square | 20.418 | 49.996 | 50.579 | 17.095 | 16.036 |
|  | p-value | 0.00004 | 0.00000 | 0.00000 | 0.00068 | 0.00112 |
| N status | Chi-square | 30.050 | 73.528 | 72.197 | 12.319 | 27.290 |
|  | p-value | 0.00000 | 0.00000 | 0.00000 | 0.00637 | 0.00001 |
| Stage of disease | Chi-square | 34.679 | 73.267 | 70.774 | 20.419 | 25.838 |
|  | p-value | 0.00001 | 0.00000 | 0.00000 | 0.00234 | 0.00024 |

*Except for the RRFS, all rates are statistically significantly correlated to cancer immunophenotype as well as with T status, N status, and the stage of the disease.*

As expected, survival rates are decreasing with the higher T and N status on the pathology report and a higher stage of the disease. However, OS, LRFS, and RRFS rates are not statistically significantly different between pN0 and pN1 and between pN2 and pN3, but among these two groups, the statistically significant difference is recorded.

All rates are also calculated for the pT1-3 pN0-1 subgroup concerning the extent of axillary surgery, demonstrating that SLNB is not inferior to ALND in terms of disease control (DFS, DDFS, LRFS, RRFS) and overall survival for this subpopulation of BC patients.

## DISCUSSION AND CONCLUSION

Development of novel anticancer drugs and increasing trend of neoadjuvant oncological ap-

*Table 3a and 3b:*

*Overall survival, local recurrence-free survival, and regional recurrence-free survival according to the N status; between N0 and N1, as well as between N2 and N3, we have found no statistically significant differences (3a), but we have found a significant difference in prognosis between N0-1 and N2-3 (3b).*

| Table 3a | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| OS | 98.11% | 97.97% | 89.66% | 82.86% |
| LRFS | 96.23% | 96.62% | 87.93% | 88.57% |
| RRFS | 97.84% | 97.97% | 87.93% | 85.71% |

| Table 3b | N0-N1 | N2-N3 | Log-Rank test | p-value |
|---|---|---|---|---|
| OS | 98.07% | 87.10% | -5.39 | 0.00000 |
| LRFS | 96.34% | 88.17% | -3.50 | 0.00046 |
| RRFS | 97.88% | 87.10% | -5.17 | 0.00000 |

*Table 4.*

*Survival rates for T1-3 N0-1 subpopulation correlate to the extent of axillary surgery; the extent of axillary surgery is not related to overall survival and locoregional control of the disease in this subpopulation of breast cancer patients.*

| | SLNB | ALND | Log-Rank test | p-value |
|---|---|---|---|---|
| OS | 99.04% | 96.11% | -2.27 | 0.02305 |
| DFS | 93.93% | 86.67% | -2.79 | 0.00520 |
| DDFS | 97.12% | 90.00% | -3.43 | 0.00060 |
| LRFS | 96.49% | 96.67% | 0.05 | 0.95813 |
| RRFS | 98.08% | 97.22% | -0.67 | 0.50231 |

proach for operable BC are leading to even less surgery. Several ongoing trials (8,9,10) aim for more de-escalation of axillary surgery for early BC patients in the primary-surgery setting.

Besides updating our institutional data, we have demonstrated that pT4 status, pN2-3 status, and stage above IIIB are related to the worst oncological outcome in the primary surgery era. The analysis also indicates that pN0 and pN1 patients have similar outcomes in terms of OS and locoregional control of disease and the pN2 and pN3 patients, but there is a statistically significant difference between pN0-1 and pN2-3 subgroups.

Moreover, according to our data, the extent of axillary surgery is not related to those outcomes in early and locally advanced (pT1-3 pN0-1) BC patients.

What might be the significance of these results translated in the neoadjuvant era? It is well known that preoperative systemic treatment does not affect OS and DFS for the whole cohort (11) but significantly improves the outcome of good responders to NAT.

The prospective observational multicenter trial, currently ongoing (12), is aiming to determine if there will be an improvement of survival rates of cN2 patients converted to ycN0 following NAT as well as the oncological safety of the ALND omission after SLNB, for initially cN1-2 patients converted to ypN0(sn) after NAT, in terms of overall survival and locoregional disease control.

Despite the reduced extent of axillary surgery, we do not expect worse oncological outcomes. Herein presented institutional data would provide the foundation for all anticipated comparations.

In addition, two ongoing randomized controlled trials, NEONOD II (13) and ATNEC (14), are yet another step ahead and are currently investigating if cN1 patients, converted to ypN+ following NAT, but with minimal residual disease in the axilla, could be safely spared of ALND with or without radiotherapy to the lymphatic drainage, i.e., investigating if the results of ACOSOG Z010 (6), IBCSG 23-01 (15) and AMAROS (5) trial results can be safely translated into the neoadjuvant setting.

Although ypN+ signifies the resistance to the systemic treatment, based on our analysis, we strongly believe in the trials mentioned above' positive outcomes and in the safe translation of conservative axillary surgery into the neoadjuvant setting.

### Author Contributions:

All authors contributed to the study conception and design. Ana Car Peterko and Manuela Avirović performed material preparation, data collection, and analysis. Ana Car Peterko wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### Statement of Ethics:

The Ethics Committee approved this research of Clinical Hospital Center Rijeka. All procedures performed in studies involving human participants followed the institutional research committee's ethical standards and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not con-

tain any studies with animals performed by any of the authors.

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Sažetak

## OPERABILNI INVAZIVNI KARCINOM DOJKE U ERI KONZERVATIVNE KIRURGIJE; RETROSPEKTIVNA ANALIZA 5-GODIŠNJEG PREŽIVLJENJA I KONTROLE BOLESTI

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*Uvod:* Temeljem suvremenih preporuka za liječenje karcinoma dojke, u Kliničkom bolničkom centru (KBC) Rijeka prihvaća se i zagovara konzervativni kirurški pristup. Međutim, na razini naše institucije, ali i na nacionalnom nivou, malo je obrađenih rezultata liječenja. Cilj ove retrospektivne analize je ažuriranje institucionalnih podataka o preživljenju i kontroli bolesti.

*Metode:* U periodu od 2011. do 2014. godine, u KBC Rijeka operirano je 915 pacijentica oboljelih od karcinoma dojke, a njih 615 uključeno je u ovu analizu. Istraživanje je odobreno od Etičkog povjerenstva KBC Rijeka.

*Rezultati:* Sve su pacijentice bile žene, prosječno stare 59 godina. Izračunate su ukupne stope preživljenja bez lokalnog, regionalnog i udaljenog recidiva, te stope ukupnog preživljenja i preživljenja bez povrata bolesti u petogodišnjem postoperativnom periodu. Sve su stope u negativnoj korelaciji sa višim T i N statusom kao i višim stadijem bolesti. Osim navedenog, rezultati su potvrdili da je biopsija sentinel limfnog čvora ekvivalentna aksilarnoj disekciji u smislu lokoregionalne kontrole bolesti kao i ukupnog petogodišnjeg preživljenja u pT1-3 pN0-1 podskupini.

*Zaključak:* Osim ažuriranja podataka naše institucije, ova je analiza potvrdila da su stope preživljenja i lokoregionalne kontrole bolesti u eri primarnog kirurškog tretmana slične između pN0 i pN1 subpopulacija kao i među pN2 i pN3, međutim statistički značajno različite između pN0-1 I pN2-3 podskupina. Prospektivno, opservacijsko, multicentrično kliničko istraživanje koje je u tijeku pokušava istražiti značenje ovih rezultata u neoadjuvantoj eri.

KLJUČNE RIJEČI: *karcinom dojke, preživljenje, recidiv*