OPTIMAL TIME FOR ADJUVANT THERAPY INITIATION IN BREAST CANCER PATIENTS: A SINGLE CENTER EXPERIENCE

Summary

Introduction. This retrospective study evaluates the association between the time of chemotherapy initiation and disease-free survival in regard to breast cancer subtypes and stage at diagnosis. Material and Methods. The study included a total of 1075 breast cancer patients, stages I – III, treated at Oncology Institute of Vojvodina, Serbia (from 2010 to 2012; n = 617). The gathered data included prognostic factors used in everyday practice. Patients were divided into three groups according to the interval between surgery and chemotherapy (≤ 30, 31 – 60, ≥ 61 days). Disease-free survival was calculated. Results. Among the 617 patients, the 5-year disease free survival estimate was similar: 81.5%, 81.0%, 84.6% (log-rank test, p = 0.728) regarding the time of adjuvant chemotherapy initiation: ≤ 30 days, 31 – 60, and ≥ 61 days, respectively. The study showed that 85% of our breast cancer patients started adjuvant chemotherapy within 3 months after definitive surgery. In multivariate analysis, independent prognostic factors for disease-free survival were nodal status and tumor size. The 5-year disease-free survival estimate was 85.8% (p = 0.001) for patients with luminal-A subtype (Estrogen +, Progesterone high, human epidermal growth factor receptor 2+, Ki-67 ≤ 20%) with a median follow-up of 62.7 months; for patients with luminal-B (Luminal B (human epidermal growth factor receptor 2+) estrogen +, human epidermal growth factor receptor 2+, Ki-67 high or Progesterone low, Luminal B (human epidermal growth factor receptor +) estrogen +, human epidermal growth factor receptor 2+, any Ki-67, any Progesterone) 78.3% (p = 0.534) with a median follow-up of 55.9 months; for patients with triple negative breast cancer it was 73.4% with a median follow-up of 58.1 months, and for patients with human epidermal growth factor receptor 2+ it was 77.1% (p = 0.448) with a median follow-up of 55.5 months. Conclusion. Early initiation of adjuvant chemotherapy is particularly important in patients with advanced-stage breast cancer at diagnosis, and those with trastuzumab-treated triple-negative breast cancer and human epidermal growth factor receptor 2-positive tumors.

Key words: Breast Neoplasms; Chemotherapy, Adjuvant; Triple Negative Breast Neoplasms; Disease-Free Survival; Receptor, ErbB-2; Treatment Outcome

Sažetak

Uvod. Ova retrospektivna studija ispituje uticaj vremena započinjanja hemoterapije na dužinu vremena bez progresije bolesti u zavisnosti od tipa karcinoma dojke i stadijuma u momentu dijagnoze. Materijal i metode. U studiji je obuhvaćeno 1 075 pacijenata oboljelih od karcinoma dojke, stadijum bolesti I–III, lećenih na Institutu za onkologiju Vojvodine, Srbija (od 2010. do 2012. godine, n = 617). Podaci su prikupljeni u odnosu na prognoščke faktore korišćene u svakodnevnoj praksi. Pacijenti su podeljeni u tri grupe podležnosti dužini vremena započinjanja hemoterapije nakon definitive hirurgije (≤ 30, 31 do 60, ≥ 61 dana). Među 617 pacijenata koji su bili uključeni, petogodišnji period bez bolesti bio je redom 81.5%, 81.0%, 84.6% (log - rank test p = 0.728), među pacijentima koji su započeli hemoterapiju ≤ 30, 31 do 60, ≥ 61 dana. Pokazano je da 85% naših pacijenata je započelo adjuvantnu hemoterapiju u tri meseca nakon završenog hirurgijskog lećenja. U multivarijantnoj analizi, nezavisni prognoščki parametri za period bez bolesti su status limfnih čvorova i veličina tumor. Petogodišnji period bez bolesti bio je redom 85.5% (p = 0.001) za luminal A-tumore (estrogen +, receptor 2 human epidermalnog faktora rasta –, Ki - 67 < 20%, progesteron visok), medijana praćenja je bila 62.7 meseci, za luminal B-tumore (luminal B receptor 2 human epidermalnog faktora rasta –) estrogen +, receptor 2 human epidermalnog faktora rasta –) estrogen +, receptor 2 human epidermalnog faktora rasta –, 78.3% (p = 0.534) 73.4% (p = 0.448) sasvim isti, kao i za trostruko negativne tumor. Zaključak. Rano započinjanje adjuvantne hemoterapije je naročito bitno za pacijente sa uznemiravajućim karcinomom dojke, za trostruko negativne i receptor 2 human epidermalnog faktora rasta pozitivne karcinome lećenе trastuzumabom.

Ključne reči: neoplasme dojke; adjuvantna hemoterapija; tripl negativni karcinom dojke; preživljanje bez bolesti; HER2+ receptori; ishod lećenja
were associated with delayed treatment [17, 18].

studies in BC [4, 15, 16]. The authors suggest that early initiation of chemotherapy in BC patients is meaningful for patients with advanced disease, TNBC, and HER2-positive tumors. It is thought that chemotherapy administration delayed beyond this time can decrease the benefit provided by cytotoxic systemic therapies [5]. Possible explanations for these effects include accelerated growth of micro-metastases after primary tumor resection, increased tumor angiogenesis, or development of primary resistance [6–10].

Meta-analysis of adjuvant chemotherapy randomized controlled trials has shown that adjuvant chemotherapy may decrease the risk of breast cancer (BC) mortality by 30 – 40% in regard to patients without chemotherapy [1]. Today, adjuvant chemotherapy is routinely recommended in 60 – 70% of BC patients after surgery. Postponing the start of adjuvant chemotherapy for more than 90 days following surgery may significantly increase the risk of death in BC patients. The optimal time for initiation of adjuvant chemotherapy after surgery is still controversial. Currently, there are no guidelines recommending the optimal time for initiation of adjuvant chemotherapy in BC patients. Retrospective studies evaluating the role of early initiation of chemotherapy reported conflicting results [2–4]. Most patients with BC start adjuvant chemotherapy within 30 to 40 days after surgery. It is thought that chemotherapy administration delayed beyond this time can decrease the benefit provided by cytotoxic systemic therapies [5]. Possible explanations for these effects include accelerated growth of micro-metastases after primary tumor resection, increased tumor angiogenesis, or development of primary resistance [6–10].

Studies differ with respect to patient and disease characteristics including the arbitrarily selected cut-off to the definition of early versus delayed beginning of therapy [11]. On the other hand, it is known that BC is a heterogeneous disease and certain subtypes of BC, such as triple negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2) positive BC are associated with worse prognosis because of increased risk of recurrence, which probably has impact on the benefit from adjuvant chemotherapy [12–14]. A most recent report from Gagliato et al. [11] indicates that the delayed adjuvant chemotherapy is particularly meaningful for patients with advanced disease, TNBC, and trastuzumab-treated HER2+ tumors.

According to the results of a retrospective study, the authors suggest that early initiation of chemotherapy is very important for the outcome of these patients [4, 15, 16]. The researchers found that factors such as socioeconmic status, health insurance coverage and ethnicity were associated with delayed treatment [17, 18].

To determine the relationship between time to chemotherapy (TTC) and survival in women with BC, we conducted a retrospective study at the Oncology Institute of Vojvodina, Serbia. It remains unclear whether TTC has a differential impact among the distinct BC subtypes. Therefore, we conducted this retrospective analysis using our single-institution data to evaluate the association between TTC and outcomes according to tumor characteristics and BC subtypes. Our country is one of the developing countries with limited financial resources for health insurance.

Material and Methods

During 2010 – 2012, there were 1075 consecutive patients who were diagnosed with stage I - III BC and underwent surgery at the Oncology Institute of Vojvodina. Patients with stage IV BC are generally treated with palliative chemotherapy and were excluded from this study. Among them, 458 were excluded for the following reasons: 236 received no adjuvant chemotherapy, 72 were having neoadjuvant chemotherapy, and 130 had inflammatory BC, unknown tumor size or surgery type, or incomplete or unknown chemotherapy or surgery data. The final study cohort included 617 patients.

Our analysis included women aged 18 to 99 years who underwent a surgical resection and adjuvant chemotherapy as initial treatment. Patients were excluded if they had not had a surgery or chemotherapy, who initiated treatment > 365 days following surgery, and those who were treated with neoadjuvant chemotherapy or radiation therapy before surgery. We examined three levels of adjuvant chemotherapy delay (≤ 30, 31 to 60, and ≥ 61 days delay). These were divided into 3 groups: less than or equal 30 days (n = 173), 31 – 60 days (n = 353) and equal or over 61 days (n = 91). The time to adjuvant chemotherapy was defined by the days from the most definitive resection of the primary site to the first administration of chemotherapy. The definitive surgical procedure at the primary site included excision biopsy, lumpectomy, and mastectomy.

We obtained information on the age at diagnosis, type of surgery, tumor pathologic stage (according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (IUAC) Tumor Node and Metastasis (TNM) classification, lymphovascular invasion (LVI), tumor grade, histology, and comorbidities. We also obtained data on estrogen receptor (ER), progesterone receptor (PgR), and HER2 status. BC subtype was defined as hormone receptor-positive (ER-positive and/or PgR-positive and HER2-negative), HER2-positive (HER2-positive regardless of hormone receptor status), and TNBC (HER2-negative and hormone receptor-negative). We identified the chemotherapy received and classified it as anthracycline-based, anthracycline and taxane-based, or other type. In addition, for the HER2-positive tumors, we further categorized them as trastuzumab-treated and non-trastuzumab treated, since the use of adjuvant trastuzumab was approved in our country in 2005.

Patients were categorized according to TTC categories, and this variable was calculated from the date of

### Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| DFS          | disease free survival |
| HER2         | human epidermal growth factor receptor 2 |
| BC           | breast cancer |
| TNBC         | triple-negative breast cancer |
| TTC          | time to chemotherapy |
| TNM          | Tumor Node and Metastasis |
| ER           | estrogen receptor |
| PgR          | progesterone receptor |
| CIs          | confidence intervals |
| CMF          | cyclophosphamide, methotrexate, fluorouracil |
| OS           | overall survival |
| ERBB2        | receptor tyrosine-protein kinase erbB-2 |
| WT           | whole time |

### Introduction

Meta-analysis of adjuvant chemotherapy randomized controlled trials has shown that adjuvant chemotherapy may decrease the risk of breast cancer (BC) mortality by 30 – 40% in regard to patients without chemotherapy [1]. Today, adjuvant chemotherapy is routinely recommended in 60 – 70% of BC patients after surgery. Postponing the start of adjuvant chemotherapy for more than 90 days following surgery may significantly increase the risk of death in BC patients. The optimal time for initiation of adjuvant chemotherapy after surgery is still controversial. Currently, there are no guidelines recommending the optimal time for initiation of adjuvant chemotherapy in BC patients.

Retrospective studies evaluating the role of early initiation of chemotherapy reported conflicting results [2–4]. Most patients with BC start adjuvant chemotherapy within 30 to 40 days after surgery. It is thought that chemotherapy administration delayed beyond this time can decrease the benefit provided by cytotoxic systemic therapies [5]. Possible explanations for these effects include accelerated growth of micro-metastases after primary tumor resection, increased tumor angiogenesis, or development of primary resistance [6–10]. Studies differ with respect to patient and disease characteristics including the arbitrarily selected cut-off to the definition of early versus delayed beginning of therapy [11]. On the other hand, it is known that BC is a heterogeneous disease and certain subtypes of BC, such as triple negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2) positive BC are associated with worse prognosis because of increased risk of recurrence, which probably has impact on the benefit from adjuvant chemotherapy [12–14]. A most recent report from Gagliato et al. [11] indicates that the delayed adjuvant chemotherapy is particularly meaningful for patients with advanced disease, TNBC, and trastuzumab-treated HER2+ tumors.

According to the results of a retrospective study, the authors suggest that early initiation of chemotherapy is very important for the outcome of these patients [4, 15, 16]. The researchers found that factors such as socioeconomic status, health insurance coverage and ethnicity were associated with delayed treatment [17, 18].

To determine the relationship between time to chemotherapy (TTC) and survival in women with BC, we conducted a retrospective study at the Oncology Institute of Vojvodina, Serbia. It remains unclear whether TTC has a differential impact among the distinct BC subtypes. Therefore, we conducted this retrospective analysis using our single-institution data to evaluate the association between TTC and outcomes according to tumor characteristics and BC subtypes. Our country is one of the developing countries with limited financial resources for health insurance.

### Material and Methods

During 2010 – 2012, there were 1075 consecutive patients who were diagnosed with stage I - III BC and underwent surgery at the Oncology Institute of Vojvodina. Patients with stage IV BC are generally treated with palliative chemotherapy and were excluded from this study. Among them, 458 were excluded for the following reasons: 236 received no adjuvant chemotherapy, 72 were having neoadjuvant chemotherapy, and 130 had inflammatory BC, unknown tumor size or surgery type, or incomplete or unknown chemotherapy or surgery data. The final study cohort included 617 patients.

Our analysis included women aged 18 to 99 years who underwent a surgical resection and adjuvant chemotherapy as initial treatment. Patients were excluded if they had no surgery or chemotherapy, who initiated treatment > 365 days following surgery, and those who were treated with neoadjuvant chemotherapy or radiation therapy before surgery. We examined three levels of adjuvant chemotherapy delay (≤ 30, 31 to 60, and ≥ 61 days delay). These were divided into 3 groups: less than or equal 30 days (n = 173), 31 – 60 days (n = 353) and equal or over 61 days (n = 91). The time to adjuvant chemotherapy was defined by the days from the most definitive resection of the primary site to the first administration of chemotherapy. The definitive surgical procedure at the primary site included excision biopsy, lumpectomy, and mastectomy.

We obtained information on the age at diagnosis, type of surgery, tumor pathologic stage (according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (IUAC) Tumor Node and Metastasis (TNM) classification, lymphovascular invasion (LVI), tumor grade, histology, and comorbidities. We also obtained data on estrogen receptor (ER), progesterone receptor (PgR), and HER2 status. BC subtype was defined as hormone receptor-positive (ER-positive and/or PgR-positive and HER2-negative), HER2-positive (HER2-positive regardless of hormone receptor status), and TNBC (HER2-negative and hormone receptor-negative). We identified the chemotherapy received and classified it as anthracycline-based, anthracycline and taxane-based, or other type. In addition, for the HER2-positive tumors, we further categorized them as trastuzumab-treated and non-trastuzumab treated, since the use of adjuvant trastuzumab was approved in our country in 2005.

Patients were categorized according to TTC categories, and this variable was calculated from the date of...
definitive surgery to the date of the first dose of adjuvant chemotherapy administration. Patients’ TTC categories were 30 days or less, 31 to 60 days, 61 or more days. Descriptive statistics were used to evaluate the characteristics of patients according to TTC, and the distribution was compared using $\chi^2$ test. The outcome of interest was disease free survival (DFS). DFS was calculated from the time of surgery to the first relapse (local, regional, and/or distant), last follow-up or death in the absence of relapse. All the patients were followed-up for at least 6 months. The Kaplan-Meier product limit method was used to estimate the 5-year DFS with 95% confidence intervals (CIs) in all patients according to TTC and other patients’ and clinical characteristics. Groups were compared by using the log-rank statistic.

Cox proportional hazards regression models were developed to determine association between TTC and survival outcomes after adjustment for potential confounders. Variables in the model included age (as a continuous variable), pathologic tumor size according to TNM classification (T1, T2, T3), pathological nodal status according to TNM classification (N1, N2, N3), histologic grade, histologic type of BC (ductal, lobular and other), presence of lymphovascular and perineural invasion, hormone receptor (ER- and PgR positive and negative), HER2 status (positive and negative), TNBC, type of surgery and presence of comorbidities. We classified the received chemotherapy as antracycline-based, antracycline/taxane-based, cyclophosphamide, methotrexate, fluorouracil (CMF) type and hormone therapy.

Results are expressed in hazard ratios and 95% CIs. P values ≤ 0.05 were considered statistically significant. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) 18.0.

The National Code on Clinical Trials has declared that ethics approval is not necessary for retrospective studies. Before this retrospective study our institutional board was informed that this study was conducted in accordance with the principles of the Declaration of Helsinki.

**Results**

The present retrospective study investigated the association between the initiation time of adjuvant chemotherapy and DFS in 617 operable BC patients. The median age at diagnosis was 55 years, and 62.4% (385) of patients were older than 50. A total of 173 (28%) patients started chemotherapy within less than 31 days; 353 (57.2%) between 31 and 60 days; and 91 (14.7%) started chemotherapy 61 or more days after surgery. Median time to initiation of adjuvant treatment was 43 days (range, 14 to 92). At the median follow-up of 54.4 months, 113 patients (18.3%) experienced distant recurrence i.e. metastases, most commonly in the bones and hepatic metastases, and 7 patients (6.2%) had experienced recurrence of BC.

| Characteristics | Interval from surgery to chemotherapy initiation (days) | p          |
|-----------------|--------------------------------------------------------|------------|
| Age, years      | ≤ 30 days, 31-60 days, ≥ 61 days                       |            |
| Median/Range    | 52/26-76, 54/25-77, 57/36-80                             |            |
| ≥ 50 years      | 50.7%/67.1%/73.6%                                        | 0.20       |
| Comorbidity     |                                                        |            |
| Absent/ Present | 75.1%/24.9%                                             | 0.003      |
| Pathologic tumor size | according to TNM classification |            |
| T1/T2/T3       | 39.9%/39.3%/36.8%                                        | 0.30       |
| Vascular/Lymphatic invasion |                         | 0.80       |
| Absent/ Present | 38.7%/61.3%                                             |            |
| Perineural invasion |                         | 0.83       |
| Absent/ Present | 53.2%/46.8%                                             |            |

**Table 1.** Patient and clinical characteristics by interval from surgery to adjuvant chemotherapy among patients with stage I to III breast cancer

**Tabela 1.** Karakteristike pacijenata i intervali započinjanja hemioterapije nakon završenog hirurškog lečenja za pacijente stadijuma I do III sa karcinomom dojke

| Characteristics | Interval from surgery to chemotherapy initiation (days) | p          |
|-----------------|--------------------------------------------------------|------------|
| Age, years      | ≤ 30 days, 31-60 days, ≥ 61 days                       |            |
| Median/Range    | 52/26-76, 54/25-77, 57/36-80                             |            |
| ≥ 50 years      | 50.7%/67.1%/73.6%                                        | 0.20       |
| Comorbidity     |                                                        |            |
| Absent/ Present | 75.1%/24.9%                                             | 0.003      |
| Pathologic tumor size | according to TNM classification |            |
| T1/T2/T3       | 39.9%/39.3%/36.8%                                        | 0.30       |
| Vascular/Lymphatic invasion |                         | 0.80       |
| Absent/ Present | 38.7%/61.3%                                             |            |
| Perineural invasion |                         | 0.83       |
| Absent/ Present | 53.2%/46.8%                                             |            |
Table 2. Survival estimate for DFS according to patient characteristics among patients with stage I to III BC treated with adjuvant chemotherapy

| Characteristic                                      | DFS (%) | p     |
|-----------------------------------------------------|---------|-------|
| **Histological grade**                              |         |       |
| GI                                                  | 9 (5.2%)| 30 (8.5%)| 10 (11.0%)| 0.50|
| GII                                                 | 67 (38.7%)| 138 (39.1%)| 32 (35.2%)|       |
| GIII                                                | 97 (56.1%)| 185 (52.4%)| 49 (53.8%)|       |
| **No. of involved lymph nodes**                     |         |       |
| 0                                                   | 73 (42.2%)| 167 (47.3%)| 38 (41.8%)| 0.31|
| 1-3                                                 | 53 (30.6%)| 93 (26.3%)| 34 (37.4%)|       |
| 3-9                                                 | 27 (15.6%)| 51 (14.4%)| 14 (15.4%)|       |
| ≥ 10                                                | 20 (11.6%)| 42 (11.9%)| 5 (5.5%)|       |
| **Histological type of breast cancer**              |         |       |
| Ductal/Duktalni                                     | 159 (91.9%)| 315 (89.2%)| 77 (84.6%)| 0.48|
| Lobular/Lobularni                                   | 5 (2.9%)| 15 (4.2%)| 6 (6.6%)|       |
| Other/Ostali tipovi                                | 9 (5.2%)| 23 (6.5%)| 8 (8.8%)|       |
| **Estrogen receptor**                              |         |       |
| Positive/Pozitivan                                  | 115 (66.5%)| 227 (64.3%)| 58 (63.7%)| 0.86|
| Negative/Negativan                                 | 58 (33.5%)| 126 (35.7%)| 33 (36.3%)|       |
| **Progesterone receptor**                          |         |       |
| Positive/Pozitivan                                  | 107 (61.8%)| 208 (58.9%)| 55 (60.4%)| 0.81|
| Negative/Negativan                                 | 66 (38.2%)| 145 (41.1%)| 36 (39.6%)|       |
| **Breast cancer subtype**                           |         |       |
| HER2-positive/HER2 pozitivan                        | 29 (16.8%)| 49 (13.9%)| 16 (17.6%)| 0.55|
| Triple-negative/Trostruko negativan                | 27 (15.6%)| 72 (20.4%)| 12 (13.2%)| 0.18|
| Hormone receptor-positive/Hormonski receptor pozitivan | 99 (57.2%)| 195 (55.2%)| 49 (53.8%)|       |
| **Surgery/Vrsta operacije**                        |         |       |
| BSC/Poštedna operacija                             | 127 (73.4%)| 269 (76.2%)| 68 (74.7%)| 0.92|
| Mastectomy/Mastektomija                            | 46 (26.6%)| 84 (23.8%)| 23 (25.3%)|       |
| **Chemotherapy/Hemioterapija**                     |         |       |
| CMF-type/CMF protokol                              | 9 (5.2%)| 22 (6.2%)| 9 (9.9%)| 0.08|
| Anthracycline-based/Antraciklinski protokol         | 58 (33.5%)| 147 (41.6%)| 34 (37.4%)|       |
| Anthracycline+Taxane/Antraciklini+Taksani           | 99 (57.2%)| 166 (47.0%)| 39 (42.9%)|       |
| Hormone therapy/Hormonska terapija                 | 7 (4.0%)| 18 (5.1%)| 9 (9.9%)|       |
| **Trastuzumab among HER2-positive patients (n= 231)** |         |       |
| Trastuzumab kod HER2-pozitivnih pacijentkinja       |         |       |
| No/Ne                                               | 28 (49.1%)| 67 (57.7%)| 26 (61.9%)| 0.09|
| Yes/Da                                             | 29 (50.9%)| 49 (42.3%)| 16 (38.1%)|       |

Legend: BSC – breast conservative surgery; CMF – cyclophosphamide, methotrexate, 5-fluorouracil; P value for different distribution in 3 groups tested by heterogeneous $x^2$ test; HER2 – receptor 2 human epidermal growth factor rasta; TNM – Tumor Nodus Metastase

Table 2. Preživljavanje pacijenata i period bez bolesti u odnosu na karakteristike pacijenata obolelih od karcinoma dojke stadijuma I do III

| Characteristic                                      | DFS (%) | p     |
|-----------------------------------------------------|---------|-------|
| **Interval from surgery to chemotherapy initiation (days)** |         |       |
| ≤ 30 days/≤ 30 dana (n = 173)                        |         |       |
| 31-60 days/31-60 dana (n = 353)                       |         |       |
| ≥ 61 days/≥ 61 dana (n = 91)                          |         |       |
| **Age ≥ 50 years/ ≥ 50 godina starosti**             | 94 (76.6%)| 226 (83.2%)| 65 (80.0%)| 0.375|
| **Age < 50 years/ < 50 godina starosti**             | 79 (87.3%)| 127 (77.2%)| 26 (96.2%)| 0.035|

Legend: $x^2$ test for unequal distribution in 3 groups; HER2 – receptor 2 human epidermal growth factor rasta; TNM – Tumor Nodus Metastase
| Comorbidity absent/Odsutni komorbiditeti | 130 | 85.4% | 247 | 81.0% | 50 | 90.0% | 0.252 |
|----------------------------------------|-----|-------|-----|-------|----|-------|--------|
| Comorbidity present/Prisutni komorbiditeti | 43  | 69.8% | 106 | 81.1% | 41 | 78.0% | 0.266 |
| Pathologic tumor size according to TNM classification/Veličina tumora prema TNM klasifikaciji | | | | | | | |
| T1 | 69 | 85.5% | 130 | 90.8% | 26 | 88.6% | 0.472 |
| T2 | 68 | 83.8% | 157 | 75.8% | 48 | 81.3% | 0.359 |
| T3 | 36 | 69.4% | 66 | 74.2% | 17 | 88.2% | 0.361 |
| Vascular/lymphatic invasion absent Odsutna vaskularna/limfna invazija | 67 | 82.1% | 145 | 86.2% | 39 | 92.3% | 0.315 |
| Vascular/lymphatic invasion present Prisutna vaskularna/limfna invazija | 106 | 81.1% | 208 | 77.4% | 52 | 78.8% | 0.778 |
| Perineural invasion absent Odsutna perineuralna invazija | 92 | 85.9% | 192 | 87.5% | 52 | 86.5% | 0.907 |
| Perineural invasion present Prisutna perineuralna invazija | 81 | 76.5% | 161 | 73.3% | 39 | 82.1% | 0.497 |
| Histological grade/Histološki gradus | | | | | | | |
| GI | 9 | 100% | 30 | 93.3% | 10 | 100% | 0.545 |
| GII | 67 | 79.1% | 138 | 83.3% | 32 | 90.6% | 0.374 |
| GIII | 97 | 81.4% | 185 | 77.3% | 49 | 77.6% | 0.753 |
| No. of involved lymph nodes/Broj zahvaćenih limfnih čvorova | | | | | | | |
| 0 | 73 | 89.0% | 167 | 89.2% | 38 | 86.8% | 0.879 |
| 1-3 | 53 | 92.5% | 93 | 83.9% | 34 | 85.3% | 0.339 |
| 4-9 | 27 | 59.3% | 51 | 72.2% | 14 | 78.6% | 0.395 |
| ≥10 | 20 | 55.0% | 42 | 52.4% | 5 | 80.6% | 0.580 |
| Histological type of breast cancer/Histološki tip karcinoma dojke | | | | | | | |
| Ductal/Duktalni | 159 | 80.5% | 315 | 81.3% | 77 | 85.7% | 0.601 |
| Lobular/Lobularni | 5 | 100% | 15 | 86.7% | 6 | 66.7% | 0.359 |
| Other/Ostali tipovi | 9 | 88.9% | 23 | 73.9% | 8 | 87.5% | 0.554 |
| ER negative/ER negativan | 58 | 70.7% | 126 | 77.0% | 33 | 81.8% | 0.437 |
| ER positive/ER pozitivan | 115 | 87.0% | 227 | 83.3% | 58 | 86.2% | 0.687 |
| PgR negative/PgR negativan | 66 | 72.7% | 145 | 76.6% | 36 | 83.3% | 0.476 |
| PgR positive/PgR pozitivan | 107 | 86.9% | 208 | 84.1% | 55 | 85.5% | 0.860 |
| HER2-positive/HER2 pozitivan | 28 | 75.0% | 42 | 85.7% | 14 | 57.7% | 0.070 |
| HER2-negative/HER2 negativan | 145 | 82.8% | 311 | 80.4% | 8 | 89.6% | 0.179 |
| Triple-negative/Trostruko negativan | 27 | 74.1% | 72 | 73.8% | 12 | 100% | 0.157 |
| Hormone receptor-positive Hormon receptor pozitivan | 99 | 87.9% | 195 | 83.6% | 49 | 83.7% | 0.658 |
| Hormone receptor-negative Hormon receptor negativan | 50 | 70.0% | 113 | 75.2% | 27 | 77.8% | 0.702 |
| Surgery/Operacija | | | | | | | |
| BSC/Poštedna | 127 | 85.6% | 269 | 83.6% | 68 | 88.6% | 0.908 |
| Mastectomy/Mastektomija | 46 | 71.7% | 84 | 73.8% | 23 | 87.0% | 0.384 |
| Chemotherapy/Hemioterapija | | | | | | | |
| CMF-type/CMF protokol | 9 | 44.4% | 22 | 90.9% | 9 | 77.8% | 0.020 |
| Anthracycline-based/Antraciklini protokol | 58 | 84.5% | 147 | 79.6% | 34 | 91.2% | 0.253 |
| Anthracycline+Taxane Antraciklini+Taksani | 99 | 81.9% | 166 | 80.1% | 39 | 79.5% | 0.963 |
| Hormone therapy/Hormonska terapija | 7 | 100% | 18 | 88.9% | 9 | 88.9% | 0.767 |
| Trastuzumab among HER2-positive patients/Trastuzumab kod HER2 pozitivnih pacijentkinja | 28 | 75.0% | 42 | 85.7% | 14 | 57.1% | 0.070 |

Legenda: DFS - period bez bolesti; ER - receptori za estrogen, PgR - receptori za progesteron, HER2 – receptor 2 humanog epidermalnog faktora rasta; CMF - ciklofosfamid, metotreksat, 5-fluorouracil, TNM – Tumor Nodus Metastaze
Table 1 lists the patients’ characteristics according to timing of adjuvant chemotherapy. Significant differences among groups were found regarding the age (p = 0.001) and comorbidity (p = 0.003). However, women with delayed chemotherapy were likely to be older and have associated diseases. Globally, 69.2% of patients presented with hormone receptor positive tumors, versus 30.8% of patients that pre-

### Table 3. Univariate analysis hazard ratio: DFS according to timing of adjuvant chemotherapy

| Variable                                | B     | HR   | CI    | p      |
|-----------------------------------------|-------|------|-------|--------|
| Age/Starost (Continuous/Kontinuirana)   | 0.002 | 0.998| 0.980-1.015 | 0.784 |
| Comorbidity/Komorbiditeti (absent vs. present/Prisutan vs odsutan) | 0.363 | 1.438 | 0.978-2.114 | 0.065 |
| Pathologic tumor size according to TNM classification/Tumorska veličina prema TNM klasifikaciji |       |      |       |        |
| T1 (Reference/Referentna vrednost)     |       |      |       |        |
| T2                                     | 0.737 | 2.091| 1.306-3.347 | 0.002 |
| T3                                     | 0.930 | 2.535| 1.490-4.313 | 0.001 |
| Vascular/lymphatic invasion (Absent vs. present/Prisutan vs odsutan) | 0.472 | 1.603 | 1.075-2.389 | 0.021 |
| Peripheral invasion (Absent vs. present/Prisutan vs odsutan) | 0.684 | 1.981 | 1.357-2.892 | 0.001 |
| Histological grade (Histološki gradus) |       |      |       |        |
| GI (Reference/Referentna vrednost)     |       |      |       |        |
| GI I                                   | 1.473 | 4.364| 1.054-18.072 | 0.042 |
| GI II                                  | 1744  | 5.722| 1.402-23.350 | 0.015 |
| No. of involved lymph nodes (Broj zahvaćenih limfnih čvorova) |       |      |       |        |
| 1-3                                    |       |      |       |        |
| 4-9                                    |       |      |       |        |
| ≥10                                    |       |      |       |        |
| Histological type of breast cancer (Histološki tip karcinoma dojke) |       |      |       |        |
| Ductal (Duktalni)                      | 0.083 | 0.921| 0.448-1.893 | 0.822 |
| Lobular (Lobularni)                    |       |      |       |        |
| Other/Ostali tipovi (Reference/Referentna vrednost) |       |      |       |        |
| Estrogen receptor (Estrogenski receptor) (Positive vs. negative/Pozitivan vs negativan) | 0.492 | 1.635 | 1.129-2.368 | 0.009 |
| Progesteron receptor (Progesteronski receptor) (Positive vs. negative/Pozitivan vs negativan) | 0.504 | 1.656 | 1.145-2.396 | 0.007 |
| HER2 receptor (HER2 receptor) (Negative vs. positive/Pozitivan vs negativan) | 0.244 | 1.276 | 0.794-2.051 | 0.314 |
| Triple-negative (Triple-negativni) (Positive vs. negative/Pozitivan vs negativan) | 0.595 | 1.813 | 1.226-2.681 | 0.003 |
| Surgery modality (Tip operacije) (BCS vs. Mastectomy/Posleđna vs mastektomija) | -0.510 | 0.600 | 0.406-0.887 | 0.010 |
| Scheme of chemotherapy used (Hemioterapijski protokol) |       |      |       |        |
| CMF-type (CMF protokol)                 | 0.950 | 2.586| 0.699-9.560 | 0.154 |
| Anthracycline-based (Antrakliinski protokol) | 0.696 | 2.006 | 0.621-6.480 | 0.245 |
| Anthracycline+Taxane (Antrakliini+ Taksani) | 0.797 | 2.220 | 0.694-7.098 | 0.179 |
| Hormone therapy (Hormonska terapija) (Reference/Referentna vrednost) |       |      |       |        |
| Hormone receptor (Hormonski receptor) (Positive vs. negative/Pozitivan vs negativan) | 0.599 | 1.820 | 1.254-2.642 | 0.002 |
| TTC, days (Vreme do započinjanja hemioterapije) |       |      |       |        |
| ≤ 30                                   |       |      |       |        |
| 31-60                                  |       |      |       |        |
| ≥61                                    |       |      |       |        |

**Legenda:** HR – odnos rizika, CI - indeks poverenja, BCS – breast conservative surgery; TNM - Tumor Nodus Metastaze; HER2 – receptor 2 humanog epidermalnog faktora rasta; CMF - ciklofosfamid, metotreksat, 5-fluouracil; B- beta
sented with hormone receptor negative tumors. However, 15.2% of patients had HER-2 positive and 23.2% TNBC. A total number of 239 (38.7%) patients received adjuvant anthracycline-based chemotherapy; 304 (49.3%) received anthracycline and taxane based chemotherapy; 40 (6.5%) received CMF-type chemotherapy; 94 (15.2%) received trastuzumab, and 343 (69%) patients received adjuvant hormone therapy. 

**Table 2** summarizes the 5-year DFS for all the investigated patients according to TTC, patients’ and tumor characteristics. Median follow-up was 54.4 months. Survival analysis, using the Kaplan-Meier method for DFS according to TTC, demonstrated that there were no differences in DFS among the groups that received adjuvant treatment at different timings (Graph 1). The 5-year DFS estimate was 81.5%, 81.0%, 84.6% (log-rank p = 0.728) among patients who initiated chemotherapy < 30 days, 31–60, and > 61 days, respectively, after surgery.

The Cox proportional hazards model was used to adjust the analysis for known prognostic factors such as age, comorbidity, pathologic tumor size, number of positive lymph nodes, vascular and perineural invasion, hormonal receptors status, tumor grade, HER-2 status, histological type of BC, surgery modality and chemotherapy regimen. In the univariate

| Variable/Varijabla | B | HR | CI 95% | p   |
|--------------------|---|----|--------|-----|
| Pathologic tumor size according to TNM classification/Tumorska veličina prema TNM klasifikaciji |   |     |        |     |
| T1 Reference/Referentna vrednost | 0.412 | 1.509 | 0.925-2.462 | 0.099 |
| T3 | 0.618 | 1.856 | 1.070-3.549 | 0.050 |
| Vascular/lymphatic invasion | Absent vs. present/odsutan vs prisutan | 0.151 | 1.163 | 0.730-1.853 | 0.525 |
| Perineural invasion | Absent vs. present/odsutan vs prisutan | 0.285 | 1.330 | 0.854-2.072 | 0.207 |
| Histological grade/Histološki gradus | Reference/Referentna vrednost | 1.138 | 3.120 | 0.742-13.128 | 0.121 |
| GI | 1.185 | 3.272 | 0.782-13.690 | 0.105 |
| No. of involved lymph nodes/Broj zahvaćenih limfnih čvorova |   |     |        |     |
| 0 Reference/Referentna vrednost | 1.381 | 3.981 | 2.320-6.830 | 0.0001 |
| 1-3 | 0.126 | 1.135 | 0.648-1.985 | 0.658 |
| 4-9 | 0.926 | 2.525 | 1.460-4.365 | 0.001 |
| ≥10 | 1.381 | 3.981 | 2.320-6.830 | 0.0001 |
| Estrogen receptor | Positive vs. negative/positivan vs negativan | -0.077 | 0.926 | 0.280-3.008 | 0.898 |
| Progesteron receptor | Positive vs. negative/positivan vs negativan | 0.181 | 1.198 | 0.587-2.443 | 0.620 |
| Triple-negative/Trostruko-negativan | Positive vs. negative/positivan vs negativan | 0.408 | 1.503 | 0.756-2.988 | 0.245 |
| Surgery modality/Tip operacije | BSC vs. Mastectomy/Poštedna vs mastektomija | -0.142 | 0.868 | 0.537-1.402 | 0.562 |
| Hormone receptor | Positive vs. negative/positivan vs negativan | 0.228 | 1.256 | 0.286-5.505 | 0.763 |

**Table 5.** Survival estimate for DFS according to breast cancer subtype among patients with stage I to III BC treated with adjuvant chemotherapy. 

| Breast cancer subtype | No. of patients | No. of events | 5-Year DFS | p   |
|-----------------------|----------------|--------------|-----------|-----|
| Luminal-A/Luminal-A    | 380            | 54           | 85.8%     | 0.001 |
| Luminal-B/Luminal-B    | 46             | 10           | 78.3%     | 0.534 |
| HER2-positive/HER2 pozitivan | 48         | 11           | 77.1%     | 0.448 |
| Triple-negative/Trostruko negativan | 143      | 38           | 73.4%     | 0.003 |

Legenda: TNM - Tumor Nodus Metastaze, CI - interval poverenja, HR - odnos rizika, B - beta
Adjuvant chemotherapy is one of the most important therapies for BC patients. The optimal time to initiate chemotherapy after surgery is still unknown. Due to the potential ethical problems it is unlikely that a prospective clinical trial will be undertaken to explore the association between delayed chemotherapy initiation and survival in BC patients. The lack of change in the attitude towards timing of adjuvant chemotherapy might be related not only to the reported controversial results, but also to the increased requests for additional testing or procedures used to decide whether or not to offer adjuvant chemotherapy [19].

All the published findings related to the treatment outcome associated with the timing of adjuvant chemotherapy initiation are retrospective. The categorization of the time of initiation as proper, early or delayed has no clinical basis, and it is based on the prejudices related to habits in the clinical practice. In clinical trials, a routine criterion for the adjuvant chemotherapy of BC is the initiation of adjuvant therapy within 6 to 8 weeks after surgical treatment, and the initiation out of this timeframe seems to be unusual and potentially harmful. The published randomized controlled clinical trials do not directly suggest the time to initiate chemotherapy after surgery. The time to therapy initiation ranges from 2 to 12 weeks in different trials [20–23]. In clinical practice, many factors may affect the time interval between surgery and adjuvant chemotherapy. Some of the frequently involved factors are related to patients’ clinical condition and comorbidities. Delays in treatment initiation are more likely to occur in Medicare patients and in low-income populations [24]. In a large, multi-institutional cohort of women with BC, time from diagnosis to initiation of adjuvant chemotherapy was approximately 12 weeks. This interval increased steadily from 10.8 to 13.3 weeks between 2003 and 2009. The greatest effects were associated with diagnostic and therapeutic interventions, including immediate post-mastectomy reconstruction, re-excision, and use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay [25].

Our study showed that 85% of BC patients started adjuvant chemotherapy within 3 months of definitive surgery. Within these 3 months, we found no association between the initiation of chemotherapy and DFS, meaning that the prognosis was similar for patients starting chemotherapy within 3 weeks after surgery and those starting chemotherapy up to 13 weeks after surgery. This is in agreement with results of other studies [26, 27]. A large population-based study did not demonstrate any benefit in overall survival (OS) from an early start of adjuvant chemotherapy among Danish BC patients treated within 3 months of definitive surgery, or for any subgroups with potentially fast growing tumors according to increasing number of involved axillary lymph nodes, increasing malignancy grade or negative hormone receptor status [3]. If chemotherapy is delayed for more than 5 months, then the concept of being adjuvant no longer holds.

Adjuvant chemotherapy decreases the risk of BC mortality through eradication of micro-metastatic tumor deposits. Some clinical studies suggest that an adjuvant chemotherapy delay for up to 12 weeks will significantly reduce the effectiveness of systemic therapy. Results of meta-analyses show that OS decreases by 13% and DFS by 14% every four weeks that adjuvant chemotherapy is delayed [28].

In regard to BC subtype, Gagliato et al. [11] and Chavez-MacGregor et al. [5] categorized patients in to hormone receptor-positive, receptor tyrosine-protein kinase erbB-2 (ERBB2) positive, and TNBC subgroups. Results showed that a WT (whole time) of 31–60 days had no significant impact on patients

**Graph 1.** Kaplan-Meier plot for disease-free survival according to interval between surgery and initiation of adjuvant chemotherapy

_Grafikon 1. Kaplan Majerova kriva za period bez bolesti u odnosu na interval koji prođe od definitivne hirurgije do početka adjuvantne terapije_
with ERBB2+ tumors or hormone receptor-positive tumors, while with TNBC, a WT 31–60 days resulted in a 26% increased risk of death. We did not find a statistically significant adverse effect on DFS among patients with ERBB2+ tumors or hormone receptor-positive tumors who had a WT longer than 60 days. In our study, all patients who were ERBB+ received trastuzumab. The HER-2 overexpression or amplification in BC is associated with worse prognosis in untreated patients and may also be associated with poor prognosis [29–31]. Also, our patients who were TNBC had statistically significantly shorter DFS. TNBC is known to have a more aggressive behavior when compared with other BC subtypes [32]. Gaglioti et al. have shown that the TNBC subgroup experienced a detrimental effect in delaying initiation of adjuvant chemotherapy in terms of OS, with a 75% and 54% increased risk of death for those women who received chemotherapy 31 to 60 days and ≥ 61 days after definitive surgery [11]. Despite the differences in OS, no differences in relapse free survival (RFS) or DFS were seen in TNBC patients [11]. It is important to mention that there is a lack of targeted therapies for this population and that chemotherapy is the only effective known treatment.

As expected, in a multivariate analysis, independent predictive factors for shorter DFS were more than 3 lymph nodes involvement and tumor size T3. In our study, there was no difference in DFS between hormone receptor positive and negative BC patients. Early initiation of chemotherapy had an impact on hormone receptor-negative patients in comparison to hormone receptor-positive patients [27]. Many trials have demonstrated that the magnitude of benefit of adjuvant chemotherapy is less pronounced among hormone receptor-positive patients [33]. Tamoxifen and aromatase inhibitors are important and effective agents in the treatment of BC and their use in adjuvant treatment reduces the risk of death and recurrence [34–36].

There is also a possibility that the detrimental effect associated with delayed TTC among hormone receptor-positive patients is related to a delay in the initiation of endocrine therapy [3].

The main limitation of this study is that it is not randomized. Despite our median follow-up of 54.4 months, it is possible that longer follow-up is needed, particularly to evaluate the effect of delay in adjuvant chemotherapy initiation among patients with hormone receptor-positive BC. Two thirds of the patients had hormone receptor–positive disease, and there was no indication that TTC for these patients made any difference at all. Endocrine manipulation may act a more positive role than earlier initiation of chemotherapy in ER positive patients.

A larger number of studies, especially those with subgroup analyses are needed. Smaller subpopulations of patients were identified in whom delays (beyond 60 days) to chemotherapy initiation might have been avoided. The magnitude of the benefit of adjuvant chemotherapy might indeed be greater in locally advanced BC, with higher probability of micro-metastatic disease, and initiation within 60 days might be an appropriate guideline for these patients. The impact also varies in regard to subtypes and an early initiation of adjuvant chemotherapy is particularly important for patients with luminal-B, TNBC and HER2+ tumors.

The recognition of the heterogeneity of BC has recently led to the concept that investigations of tailored adjuvant treatment in specific subpopulations, through international collaboration, are the key to improve the outcome in patients with early BC.

**Conclusion**

In conclusion, our retrospective study did not show that the timing of adjuvant chemotherapy initiation affected the outcome in patients with early breast cancer. The current report suggests that unnecessary delay in initiation of chemotherapy may be unwise in patients in whom the effect of adjuvant chemotherapy is expected to be significant. Early initiation of adjuvant chemotherapy is particularly relevant in patients with advanced-stage breast cancer at diagnosis, those with triple-negative breast cancer, and patients with trastuzumab-treated human epidermal growth factor receptor 2-positive tumors. Since the realization of a prospective trial that should definitely provide reliable data seems to be unlikely, only retrospective trials with sufficient statistical power and valuable data, to detect differences among groups, can help to explain this interesting issue.

**References**

1. Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.

2. Shannon C, Ashley S, Smith IE. Does timing of adjuvant chemotherapy for early breast cancer influence survival? J Clin Oncol. 2003;21(20):3792-7.

3. Cold S, Dürring M, Ewertz M, Knoop A, Möller S. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). Br J Cancer. 2005;93(6):627-32.

4. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-breast cancer. J Clin Oncol. 2006;24(30):4888-94.

5. Chavez-MacGregor M, Clarke CA, Lichtensztein DY, Giordano SH. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2(3):322-9.

6. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. Cancer Res.1989;49(8):1996-2001.

7. Folkman J. Endothelial cells and angiogenic growth factors in cancer growth and metastasis. Introduction. Cancer Metastasis Rev. 1990;9(3):171-4.

8. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep. 1979;63(11-12):1727-33.
follow-up results of French Adjuvant Study group 05 randonized trial. J Clin Oncol. 2001;19(3):602-11.
24. Bleicher RJ, Ruth K, Sigurdson ER, Ross E, Wong YN, Patel SA, et al. Preoperative delays in the US Medicare population with breast cancer. J Clin Oncol. 2012;30(36):4485-92.
25. Vandergrift JL, Niland JC, Theriault RL, Edge SB, Wong YN, Loftus LS, et al. Time to adjuvant chemotherapy for breast cancer in National Comprehensive Cancer Network institutions. J Natl Cancer Inst. 2013;105(2):104-12.
26. Buздaz AU, Smith TL, Powell KC, Blumenschein GR, Gehan EA. Effect of timing of initiation of adjuvant chemo-therapy on disease-free survival in breast cancer. Breast Cancer Res Treat. 1982;2(2):163-9.
27. Colleoni M, Bonetti M, Coates AS, Castiglione-Gertsch M, Gelber RD, Price K, et al. Early start of adjuvant che-motherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen recep-tors. The International Breast Cancer Study Group. J Clin Oncol. 2000;18(3):584-90.
28. Zhan QH, Fu JQ, Fu FM, Zhang J, Wang C. Survival and time to initiation of adjuvant chemotherapy among breast cancer patients: a systematic review and meta-analysis. Oncotarget. 2018;9(2):2739-51.
29. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177-82.
30. Paik S, Hazan R, Fisher ER, Sass RE, Fisher B, Redmond C, et al. Pathologic findings from the National Adjuvant Breast and Bowel Project: prognostic significance of erbB-2 protein overexpression in primary breast cancer. J Clin Oncol. 1990;8(1):103-12.
31. Gilcrease MZ, Woodward WA, Nicolas MM, Corley LJ, Fuller GN, Esteve FJ, et al. Even low-level HER2 expression may be associated with worse outcome in node-positive breast cancer. Am J Surg Pathol. 2009;33(5):759-67.
32. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.
33. Joensuu H, Kellocalous-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354(8):809-20.
34. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002;359(9324):2131-9.
35. Goss PE, Ingle JN, Martinos S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmeno-pausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349(19):1793-802.
36. Coombes RC, Hall E, Gibson LJ, Paaridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004;350(11):1081-92.