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Triple negative breast cancer

Trojno negativni rak dojk

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Abstract

Triple negative breast cancer (TNBC) represents 10–20% of all breast cancer types and is characterized by the lack of expression of oestrogen receptors, progesterone receptors and HER2 receptor. If the tumour is negative also for androgen receptors, it is called quadruple negative breast cancer. TNBC differs in many ways from other types of breast cancer. The incidence is higher in Afro-Americans and younger women. Histologically, tumours are mainly high-grade invasive ductal carcinomas. Systemic spread is more common than local recurrence, and there are more visceral metastases. Compared to other types of breast cancer, time to disease recurrence is shorter and overall survival is worse. The only effective standard systemic treatment is chemotherapy. PARP inhibitors and immunotherapy show promising results in some subtypes of TNBC. Several clinical trials are still ongoing.

Izvleček

Trojno negativni rak dojk (TNRD) predstavlja 10–20 % vseh primerov raka dojk. Zanj je značilno, da estrogenski receptorji, progesteronski receptorji in receptor HER2 niso izraženi. Kadar je tumor negativen tudi za androgene receptorje, govorimo o četverno negativnem raku dojk. TNRD se v številnih lastnostih razlikuje od ostalih tipov raka dojk. Incidenca je višja pri Afroameričankah in mlajših ženskah. Histološko gre večinoma za invazivne duktalne karcinome, ki so v večjem deležu slabo diferencirani. Pogosteje pride do sistemskega razsoja bolezni kot pa do lokalnega recidiva. Pogosteje kot ostale vrste raka dojk zaseva v visceralne organe. Slabše je celokupno preživetje, čas do ponovitve bolezni pa je krajši. Edino učinkovito standardno sistemsko zdravljenje je kemoterapija. Med novejšimi zdravili za zdravljenje TNRD kažejo svojo učinkovitost zaviralci PARP in imunoterapija, vendar le pri določenih podtipih TNRD. Številne klinične raziskave na tem področju že potekajo.

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1 Introduction

According to the Cancer Registry of the Republic of Slovenia for 2016, breast cancer is (with the exception of non-melanoma skin cancer) by far the most common cancer in women in Slovenia (1). In 2016, 1,386 women were newly diagnosed with breast cancer in Slovenia. This means the incidence is 133.2 per 100,000 women (1).

One of the types of breast cancer is triple-negative breast cancer (TNBC). This is a heterogeneous group of cancer cases characterized by the fact that they are negative for expression of oestrogen receptors, progesterone receptors and the human epidermal growth factor receptor 2 (HER2). TNBC has a more aggressive behaviour and worse survival (2).

2 Epidemiology and aetiology

TNBC accounts for 10–20% of all breast cancer cases (3-8). The incidence of the disease is higher in African-American women and younger women (8,9). Data analyses from the California Cancer Registry collected between 1988 and 2006 showed that TNBC is more common in African-American women compared to other races in all age groups. The analyses also show that the incidence of other types of breast cancer increases with age, while the incidence of TNBC is constantly below 50 cases per 100,000 women. The plateau in the incidence of TNBC occurs after the age of 60 (10). A larger study, which included 2,658 breast cancer patients (of which 554 had TNBC) and 2,448 controls, investigated the link between reproductive factors and TNBC and found that breastfeeding reduces the risk of TNBC; age at menarche, age at first birth, and number of births were not associated with the risk of TNBC (11). Unlike other types of breast cancer, TNBC is not associated with age at menopause, menopausal status, and type of menopause. Also, the use of exogenous hormones – oral contraception and hormone replacement therapy – does not seem to be associated with TNBC. A positive family history increases the risk of all types of breast cancer (9). The link between TNBC and obesity, however, remains controversial. A meta-analysis published by Pierobon et al. in 2013 showed that obese women (body mass index – BMI >30) had a 20% higher risk of TNBC compared to women with BMI <30 (12). Another study found that 50% of women with TNBC were obese, while this proportion was lower in other types of breast cancer at 36% (13). A later study published in 2015, which included African-American women, did not confirm this. However, they found that higher BMI (>35) in postmenopausal women was associated with a lower risk of TNBC, and in younger women, BMI was not associated with the incidence of TNBC compared to other types of breast cancer (14).

Due to the aggressive course of the disease, TNBC, despite the smaller proportion among breast cancer types, is responsible for a large proportion of deaths associated with this disease (8). A retrospective study published by Dent et al. found that women with TNBC were younger at diagnosis, had a higher risk of recurrence and of death within 5 years of diagnosis, but not later. Also, in patients with TNBC, the tumours were larger compared to tumours of other types of breast cancer at diagnosis (5).

BRCA 1 and BRCA 2 are tumour suppressor genes involved in repairing DNA damage. Mutations in these genes increase the chance of developing breast cancer. In 2018, a meta-analysis that examined the relationship between BRCA status and TNBC was published. It showed that TNBC is more common in patients with the BRCA 1 mutation compared to carriers of the BRCA 2 mutation and in those without the mutation (15). Among carriers of the BRCA 1 mutation who are diagnosed with breast cancer, 70% are TNBCs (16). Mutations in BRCA 1 and BRCA 2 occur in 3.4% of breast cancers (17) and up to 37% in TNBC (18,19).

3 Characteristics, histological examinations and classification of TNBC

As with all types of breast cancer, the vast majority (approximately 95%) of TNBCs are histologically invasive ductal carcinomas. Other histological types include medullary carcinoma, lobular carcinoma, metaplastic carcinoma, and other rarer types (2,20,21).

Diagnosis of TNBC is based on determining the status of hormone receptors (HR) and the HER2 receptor on samples of core needle biopsies or on samples of removed tumours. Determination of oestrogen receptors (ER) and progesterone receptors (PR) in breast cancer is immunohistochemical. The HR and the HER2 status are determined in accredited laboratories in accordance with the recommendations of the American Society of Clinical Oncology (ASCO) and

the College of American Pathologists (CAP), which set out precise protocols for tissue preparation and evaluation of samples (22,23). It is important that the time from tissue acquisition to fixation should be as short as possible and the samples should be sliced at 5-mm intervals. The laboratory must have a precise record of the time the samples are processed, and must also have internal and external quality control. When receptors on the nucleus of tumour cells are present in 1–100% of breast cancer tissue samples, the result is defined as a hormone-positive tumour. The proportion of positive cells must be stated in the pathohistological report. The efficacy of hormone therapy is corresponding to the proportion of hormone-positive cells, so in the case where receptors are present in only 1–10% of cells, we speak of low-positive tumours. Particularly in such cases, quality control is important, as data on the effectiveness of hormone therapy in low-positive tumours are limited. A tumour is hormone receptor negative when hormone receptors are present in less than 1% of cells (22,24). It is important that the percentage reflects the number of positive cells in the whole sample, not just the areas with the highest expression (24).

The HER2 gene encodes a growth factor receptor and is amplified in about 15% of breast cancers (25). HER2 status is determined immunohistochemically and/or by fluorescence *in situ* hybridization (FISH). When a tumour is immunohistochemically negative or has a weak membrane immunohistochemical reaction and a normal number of HER2 genes, we speak of a HER2-negative tumour (23,25). Immunohistochemically, tumours are classified according to the proportion of stained cells into four groups: negative reaction (0), weak positive reaction (1+), moderate positive reaction (2+) and positive (3+) reaction. When the reaction is 0 or 1+, the tumour is HER2 negative and when it is 3+, it is positive. In the case of 2+, the result is considered borderline, so *in situ* hybridization is necessary (23).

Although the diagnosis is made immunohistochemically based on the absence of receptors, TNBC also has certain typical histological features. Within the tumour, areas of necrosis and connective tissue proliferation are common, and lymphocyte infiltration is present, which is also more pronounced in the tissue around the tumour (20,21). It is the lymphocytes that infiltrate tumour tissue (tumour infiltrating lymphocytes; TIL) that are becoming an increasingly important prognostic marker. The presence of many TIL in TNBC is associated with a better response to adjuvant and neoadjuvant chemotherapy, as well as prolonged survival and time to progression (24). TNBCs are more often poorly differentiated compared to other types of breast cancer and are mostly basal-like (17).

Based on gene expression, TNBC can be divided into four subtypes: basal-like 1 and 2 (differing in immune response), mesenchymal, and luminal androgen. Individual subtypes are differently sensitive to chemotherapy and also differ in survival. Based on the analysis of DNA and RNA profiles, TNBC is divided into four subtypes: luminal androgen, mesenchymal, basal-like immune-suppressed subtype and basal-like immune-activated. Each subtype has certain specific treatment targets (e.g. androgen receptor in the luminal androgen subtype) and a different prognosis (e.g. a basal-like immune-activated type has a better prognosis than the immune-suppressed one) (24).

For TNBC, in which androgen receptors (AR) are also absent, the term quadruple-negative breast cancer (QNBC) is used in the literature. These are 10–50% of all TNBCs (26,27).

The impact of AR on TNBC prognosis is not entirely clear, although most data suggest that the presence of AR is associated with better prognosis. The rate of pathological complete responses to neoadjuvant chemotherapy is lower in TNBCs with expressed AR, but the time to disease recurrence is longer and overall survival is better (27). In clinical trials, AR is being considered as a possible target for treatment with antiandrogenic drugs (bicalutamide, enzalutamide) and cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17) enzyme inhibitors such as abiraterone acetate (28), but clear conclusions which would affect clinical practice are not yet available.

4 Clinical features and imaging

Due to the faster growth of TNBC – compared to other types of breast cancer – this type of cancer is more often detected clinically than during mammography as part of a screening programme (8). This is also due to the fact that TNBC mainly affects younger women who are not included in breast cancer screening programmes.

On mammography, TNBC is presented as a tumour mass, usually without the characteristic calcifications (20). Several studies have compared the characteristics of TNBC and other types of breast cancer according to a series of imaging studies. A study published by Kim et al. in 2013 showed that TNBC is presented on a mammogram as a hyperdense tumour mass (89%), oval (69%) or lobular (29%) in shape, with indistinct

(43%) or circumscribed (32%) margins (29). In other types of breast cancer, the margins are often irregularly shaped, spiculated, with calcifications present (20). According to data published in 2008 by Yang et al., calcifications in TNBC were present in 15% of tumours and in more than 60% in other types of breast cancer (30,31).

The ultrasound shows TNBC as a hypodense structure without microcalcifications (20). According to data from the aforementioned Kim study, TNBC was a hypoechoic mass (82%), irregular (69%) or oval (29%) in shape, with circumscribed (18%) or indistinct (18%) margins. Paralel tumour orientation (69%) was also characteristic (29). Posterior acoustic shadow is also described in the literature as one of the characteristics of a malignant breast tumour. But opinions on this are divided. In some cases, it has been found to be present in only 5% of TNBCs (31) and, according to other data, in up to 40% (20). Ultrasound examination is particularly important in women under the age of 35, and in case of suspicious abnormalities at mammogram (32). In addition, magnetic resonance imaging (MRI) can also be used for imaging (20).

The diagnosis of TNBC is made on the basis of a histological examination of the primary tumour, although the degree of HR expression and HER2 status can also be determined in samples of fine-needle biopsies by cytological examination. However, such a method is suitable only in diagnosing metastases (32).

5 Metastases and survival

In the way the disease recurs, TNBC differs from other types of breast cancer. TNBC has the highest rates of distant metastases in the timeframe of three to five years from the time of diagnosis and then rapidly subsides; this is in contrast to other types of breast cancer, in which there is no apparent decline in the risk of disease recurrence (5,8,33). Systemic recurrence is more common than local recurrence (20). With the appearance of distant metastases local recurrence is rarely present. In addition, a conclusion about the occurrence of distant metastases cannot be made on the basis of local recurrence in TNBC (5). The mean time to disease recurrence is 1.2 years shorter in TNBC than in other types of breast cancer (34). According to a Slovenian study published in 2011 by Ovčariček et al. showing 269 TNBC patients treated at the Institute of Oncology in Ljubljana between March 2000 and December 2006, systemic recurrences predominated in 92%, while exclusively local recurrences of the disease were rare and occurred in 2% (33).

TNBC patients have an increase incidence of visceral metastases compared with other types of breast cancer (11,33). The results of a study published by Dent et al. showed that within five years of diagnosis bone metastases occurred with about the same frequency in TNBC as in other types of breast cancer, whereas visceral metastases occurred four times as often in TNBC (35). A 2013 study by Tsenga et al. found that in TNBC the first site of distant metastases was bones in 22.9%, lungs in 20%, liver in 13.7%, pleura in 8.8%, and brain in 6.8%. 18% of patients had metastases at multiple sites when they were diagnosed with the systemic recurrence (36).

The average survival after recurrence was 9 months, according to a study by Dent et al. (5). According to a retrospective study published in 2009 by Kassam et al., which included 111 patients with TNBC that had metastasized, the median survival was 13.3 months (37).

The aggressive characteristics of TNBC (higher degree of differentiation, larger size of the tumour at diagnosis, higher Ki-67 expression) are most likely the main reason for poorer overall survival and shorter time to disease recurrence. The high risk of recurrence of TNBC decreases with age and is almost the same after five years as with other types of breast cancer (34).

In the aforementioned Slovenian study, the 5-year overall survival was 74.5% and the 5-year-disease-free survival was 68.2% (33). Similar findings were shown by a larger study published by James et al. in 2018, covering 1,390 patients with TNBC. A 5-year survival was 72% and a 10-year survival was 61%, considering that there were no distant metastases at diagnosis. This study also found that 69.8% of patients were disease-free after 5 years and 60.9% after 10 years (38). A small retrospective study published by Gonçalves et al. in 2018, which included 447 breast cancer patients, shows a 5-year survival and disease-free survival 62.1% and 57.5% for TNBC compared to 80.8% and 75.3% in other types of breast cancer (39).

6 Systemic treatment

6.1 Standard treatment

Due to the absence of hormone receptors and HER2 receptors, treatment with conventional cytostatics is the only effective standard systemic treatment. Anthracyclines and taxanes are used in adjuvant treatment. Several studies have shown that platinum derivatives are effective in the treatment of TNBC in patients with the BRCA mutation in neoadjuvant regimen. There

is currently no strong evidence to support the use of platinum derivatives in the adjuvant treatment of all TNBCs (40-42). According to the recommendations of the European Society for Medical Oncology (ESMO), platinum derivatives are not routinely used, but are suitable for selected young patients carrying BRCA 1 and BRCA 2 mutations with larger tumours (43,44). For TNBC stage II and III, European and Slovenian guidelines recommend neoadjuvant chemotherapy (43,45). As a recent meta-analysis has shown, a pathological complete response after neoadjuvant chemotherapy, especially in TNBC, is associated with a significantly longer period of disease-free survival and overall survivall. In patients with TNBC who achieved a pathologically complete response with neoadjuvant chemotherapy, the 5-year survival was 90%, and in those who had residual disease present after neoadjuvant chemotherapy, only 57% (46). In patients who do not achieve a pathological complete response with neoadjuvant chemotherapy with anthracyclines and taxanes, it is sensible to add adjuvant treatment with capecitabine. A prospective CREATE-X study showed that disease-free survival was significantly longer in patients receiving capecitabine (69.8%) compared to the control group (51.6%). Overall survival was also better (80.8% vs. 70.3%) (47). On the other hand, data from the CIBOMA/GEICAM study published at the end of 2018 did not confirm the benefit of capecitabine after neoadjuvant treatment for all TNBCs. Significantly better results regarding disease-free survival and the overall survival were shown only for the non-basal-like TNBC subgroup (48).

Treatment of metastatic TNBC depends on a variety of factors, notably the localization of the metastases, prior treatment, and the general condition of the patient. The choice of cytostatics is therefore individual. Given that TNBC most often disseminates to visceral organs and is usually aggressive, it is often sensible to use combinations of cytostatics instead of a monotherapy (42).

6.2 Treating patients with BRCA 1 and BRCA 2 mutations with PARP inhibitors

PARP inhibitors are drugs that inhibit the enzyme poly(adenosine diphosphate-ribose) polymerase (PARP). Tumour cells with the BRCA 1 and BRCA 2 mutations need PARP to repair defects that occur during single-strand division. Healthy cells eliminate such defects by other mechanisms, so PARP inhibitors have no significant effect on them.

The OlympiAD clinical trial compared the efficacy of standard mono-chemotherapy and the PARP inhibitor olaparib in patients with the BRCA 1 or BRCA 2 mutation with metastatic breast cancer. In the group receiving olaparib, 45.3% of patients had TNBC. The response to treatment was better in patients receiving olaparib (59.9%) compared to patients receiving standard chemotherapy (28.8%), and there was a longer disease-free survival (7.0 months vs. 4.2 months) (49). Based on this study, the US Food and Drug Administration (FDA) approved olaparib for the treatment of advanced, HER2-negative breast cancer in carriers of the BRCA 1 and BRCA 2 mutations in early 2018, and the European Medicines Agency (EMA) a year later.

The largest study in the treatment of metastatic breast cancer with PARP inhibitors is the EMBRACA study, which evaluated the efficacy of talazoparib. In patients with talazoparib, the time to progression was statistically significantly longer than in the group receiving standard chemotherapy (8.6 vs. 5.6 months). Among those receiving talazoparib, half of the patients (49.8%) had TNBC (50). However, the latest results of this study, published in the spring of 2020 at a meeting of the American Association for Cancer Research (AACR), showed that there were no differences in overall survival between the group receiving talazoparib and the control group (51).

The efficacy of new PARP inhibitors such as veliparib and rucaparib is currently being studied.

6.3 Immunotherapy

In recent years, more emphasis is being put on the importance of the immune system in the course of TNBC. Among the newer drugs that have shown efficacy in clinical trials is the monoclonal antibody atezolizumab, which acts on the PD-L1 protein (programmed cell death ligand-1). PD-L1 binds to PD-1 (programmed cell death protein-1), which is present on T lymphocytes, thereby inhibiting the immune response. Increased expression of PD-L1 on some tumour cells ensures that tumour cells avoid an immune response (52,53).

The IMpassion 130 clinical trial compared the efficacy of atezolizumab in combination with the cytostatics nab-paclitaxel and nab-paclitaxel with placebo in patients with metastatic TNBC who had not previously been treated with systemic therapy. After a good year of follow-up, the median time to progression was longer in the group receiving atezolizumab (7.2 vs. 5.5 months), with a slightly larger difference in the

PD-L1-positive tumour subgroup (7.5 vs. 5.0 months), in which a significantly longer survival was also recorded (25.0 vs. 15.5 months) (54). The results of long-term follow-up confirm benefit in the PD-L1 positive group only, so in March 2019, the US FDA approved atezolizumab in combination with the cytostatic nab-paclitaxel for advanced forms of TNBC in PD-L1-positive patients. In Europe, this medicine for the treatment of breast cancer has not yet been approved.

6.4 Potential new systemic treatment options

Researchers' efforts are focused on searching for new potential TNBC-specific targets for therapy. The PI3K-Akt-mTOR cell signalling pathway, the MAPK signalling pathway, epidermal growth factor (EGRF), vascular endothelial growth factor (VEGF), androgen receptors, proteases, and others are being studied (44,55). Research in this area is mainly in the early stages. The road to the use of such new drugs in clinical practice will therefore be a long one.

7 Conclusion

TNBC is known to be the more aggressive type of breast cancer – one that affects younger women, has poorer prognosis and does not yet have an established targeted treatment. Nevertheless, knowledge about this type of cancer has greatly expanded. It is clear that this is a heterogeneous disease with several subtypes, each with its own genetic and molecular characteristics, and thus a potential for new targeted treatment.

Conflict of interest

None declared.

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References

1. Rak v Sloveniji 2016. Ljubljana: Onkološki inštitut, Epidemiologija raka in reister raka, Register raka Republike Slovenije; 2019.
2. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Trojni negativni rak dojke: izzivi in priložnosti heterogene bolezni. Nat Rev Clin Oncol. 2016;13(11):674-90. DOI: 10.1038/nrclinonc.2016.66 PMID: 27184417
3. Kumar P, Aggarwal R. An overview of triple-negative breast cancer. Arch Gynecol Obstet. 2016;293(2):247-69. DOI: 10.1007/s00404-015-3859-y PMID: 26341644
4. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer. 2007;110(4):876-84. DOI: 10.1002/cncr.22836 PMID: 17620276
5. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429-34. DOI: 10.1158/1078-0432.CCR-06-3045 PMID: 17671126
6. Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J Natl Cancer Inst. 2015;107(6). DOI: 10.1093/jnci/djv048 PMID: 25825511
7. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007;109(1):25-32. DOI: 10.1002/cncr.22381 PMID: 17146782
8. Podo F, Buydens LM, Degani H, Hilhorst R, Klipp E, Gribbestad IS, et al.; FEMME Consortium. Triple-negative breast cancer: present challenges and new perspectives. Mol Oncol. 2010;4(3):209-29. DOI: 10.1016/j.molonc.2010.04.006 PMID: 20537966
9. Gierach GL, Burke A, Anderson WF. Epidemiology of triple negative breast cancers. Breast Dis. 2010;32(1-2):5-24. DOI: 10.3233/BD-2010-0319 PMID: 21965309
10. Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women : implications for breast cancer screening recommendations. Cancer. 2011;117(12):2747-53. DOI: 10.1002/cncr.25862 PMID: 21656753
11. Ma H, Ursin G, Xu X, Lee E, Togawa K, Duan L, et al. Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. Breast Cancer Res. 2017;19(1):6. DOI: 10.1186/s13058-016-0799-9 PMID: 28086982
12. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;137(1):307-14. DOI: 10.1007/s10549-012-2339-3 PMID: 23179600
13. Vona-Davis L, Rose DP, Hazard H, Howard-McNatt M, Adkins F, Partin J, et al. Triple-negative breast cancer and obesity in a rural Appalachian population. Cancer Epidemiol Biomarkers Prev. 2008;17(12):3319-24. DOI: 10.1158/1055-9965.EPI-08-0544 PMID: 19064545
14. Bandera EV, Chandran U, Hong CC, Troester MA, Bethea TN, Adams-Campbell LL, et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. Breast Cancer Res Treat. 2015;150(3):655-66. DOI: 10.1007/s10549-015-3353-z PMID: 25809092
15. Chen H, Wu J, Zhang Z, Tang Y, Li X, Liu S, et al. Association Between BRCA Status and Triple-Negative Breast Cancer: A Meta-Analysis. 2018;9:909. DOI: 10.3389/fphar.2018.00909 PMID: 30186165

16. Stevens KN, Vachon CM, Couch FJ. Genetic susceptibility to triple-negative breast cancer. Cancer Res. 2013;73(7):2025-30. DOI: 10.1158/0008-5472.CAN-12-1699 PMID: 23536562
17. Baretta Z, Mocellin S, Goldin E, Olopade OI, Huo D. Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine (Baltimore). 2016;95(40):e4975. DOI: 10.1097/MD.0000000000004975 PMID: 27749552
18. Geredeli C, Yasar N, Sakin A. Germline Mutations in BRCA1 and BRCA2 in Breast Cancer Patients with High Genetic Risk in Turkish Population. Int J Breast Cancer. 2019;2019:9645147. DOI: 10.1155/2019/9645147 PMID: 30713775
19. Pogoda K, Niwińska A, Sarnowska E, Nowakowska D, Jagiełło-Gruszfeld A, Siedlecki J, et al. Effects of BRCA Germline Mutations on Triple-Negative Breast Cancer Prognosis. J Oncol. 2020;2020:8545643. DOI: 10.1155/2020/8545643 PMID: 32322271
20. Schmadeka R, Harmon BE, Singh M. Triple-negative breast carcinoma: current and emerging concepts. Am J Clin Pathol. 2014;141(4):462-77. DOI: 10.1309/AJCPQN8GZ8SILKGN PMID: 24619745
21. Elsawaf Z, Sinn HP. Triple-Negative Breast Cancer: Clinical and Histological Correlations. Breast Care (Basel). 2011;6(4):273-8. DOI: 10.1159/000331643 PMID: 22135625
22. Allison KH, Hammond ME, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020;38(12):1346-66. DOI: 10.1200/JCO.19.02309 PMID: 31928404
23. Wolff AC, Hammond ME, Allison KH, Harvey BE, Mangu PB, Bartlett JM, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105-22. DOI: 10.1200/JCO.2018.77.8738 PMID: 29846122
24. WHO Classification of Tumours Editorial BoardBreast tumours. Lyon: International Agency for Research on Cancer; 2019. pp. 82-101, 268-74.
25. Gazić B, Kloboves Prevodnik V. Histopatološke in citopatološke značilnosti raka dojk. In: Takač I. Ginekološka onkologija. Maribor: Univerzitetna založba univerze; 2020. pp. 789-800.
26. Gerratana L, Basile D, Buono G, De Placido S, Giuliano M, Minichillo S, et al. Androgen receptor in triple negative breast cancer: A potential target for the targetless subtype. Cancer Treat Rev. 2018;68:102-10. DOI: 10.1016/j.ctrv.2018.06.005 PMID: 29940524
27. Bhatarai S, Klimov S, Mittal K, Krishnamurti U, Li X, Oprea-Ilies G, et al. Prognostic role of androgen receptor in triple negative breast cancer: A multi-institutional study. Cancers (Basel). 2019;11(7):995. DOI: 10.3390/cancers11070995
28. Mina A, Yoder R, Sharma P. Targeting the androgen receptor in triple-negative breast cancer: current perspectives. OncoTargets Ther. 2017;10:4675-85. DOI: 10.2147/OTT.S126051 PMID: 29033586
29. Kim MY, Choi N. Mammographic and ultrasonographic features of triple-negative breast cancer: a comparison with other breast cancer subtypes. Acta Radiol. 2013;54(8):889-94. DOI: 10.1177/0284185113488580 PMID: 23761558
30. Yang WT, Dryden M, Broglio K, Gilcrease M, Dawood S, Dempsey PJ, et al. Mammographic features of triple receptor-negative primary breast cancers in young premenopausal women. Breast Cancer Res Treat. 2008;111(3):405-10. DOI: 10.1007/s10549-007-9810-6 PMID: 18026834
31. Ko ES, Lee BH, Kim HA, Noh WC, Kim MS, Lee SA. Triple-negative breast cancer: correlation between imaging and pathological findings. Eur Radiol. 2010;20(5):1111-7. DOI: 10.1007/s00330-009-1656-3 PMID: 19898850
32. Žgajnar J, Marinko T, Šeruga B. Rak dojk. In: Strojan P, Hočevar M. Ljubljana: Onkološki inštitut; 2018. pp. 889-94.
33. Ovčariček T, Frkovic SG, Matos E, Možina B, Borštnar S. Triple negative breast cancer - prognostic factors and survival. Radiol Oncol. 2011;45(1):46-52. DOI: 10.2478/v10019-010-0054-4 PMID: 22933934
34. de Ruijter TC, Veeck J, de Hoon JP, van Engeland M, Tjan-Heijnen VC. Characteristics of triple-negative breast cancer. J Cancer Res Clin Oncol. 2011;137(2):183-92. DOI: 10.1007/s00432-010-0957-x PMID: 21069385
35. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat. 2009;115(2):423-8. DOI: 10.1007/s10549-008-0086-2 PMID: 18543098
36. Tseng LM, Hsu NC, Chen SC, Lu YS, Lin CH, Chang DY, et al. Distant metastasis in triple-negative breast cancer. Neoplasma. 2013;60(3):290-4. DOI: 10.4149/neo_2013_038 PMID: 23373998
37. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer. 2009;9(1):29-33. DOI: 10.3816/CBC.2009.n.005 PMID: 19299237
38. James M, Dixit A, Robinson B, Frampton C, Davey V. Outcomes for Patients with Non-metastatic Triple-negative Breast Cancer in New Zealand. Clin Oncol (R Coll Radiol). 2019;31(1):17-24. DOI: 10.1016/j.clon.2018.09.006 PMID: 30274766
39. Gonçalves H, Guerra MR, Duarte Cintra JR, Fayer VA, Brum IV, Bustamante Teixeira MT. Survival Study of Triple-Negative and Non-Triple-Negative Breast Cancer in a Brazilian Cohort. Clin Med Insights Oncol. 2018;12:1179554918790563. DOI: 10.1177/1179554918790563 PMID: 30083066
40. Caramelo O, Silva C, Caramelo F, Frutuoso C, Almeida-Santos T. The effect of neoadjuvant platinum-based chemotherapy in BRCA mutated triple negative breast cancers -systematic review and meta-analysis. Hered Cancer Clin Pract. 2019;17(1):11. DOI: 10.1186/s13053-019-0111-y PMID: 30962858
41. Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497-508. DOI: 10.1093/annonc/mdy127 PMID: 29873695
42. Lebert JM, Lester R, Powell E, Seal M, McCarthy J. Advances in the systemic treatment of triple-negative breast cancer. Curr Oncol. 2018;25(11):S142-50. DOI: 10.3747/co.25.3954 PMID: 29910657
43. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al.; ESMO Guidelines Committee. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(10):1674. DOI: 10.1093/annonc/mdz189 PMID: 31236598
44. Park JH, Ahn JH, Kim SB. How shall we treat early triple-negative breast cancer (TNBC): from the current standard to upcoming immuno-molecular strategies. ESMO Open. 2018;3:e000357. DOI: 10.1136/esmoopen-2018-000357 PMID: 29765774
45. Perhavec A. Smernice diagnostike in zdravljenja raka dojk. Ljubljana: Onkološki inštitut; 2018 [cited 2019 Sep 23]. Available from: https://www.onko-i.si/fileadmin/onko/datoteke/Smernice/Smernice_diagnostike_in_zdravljenja_raka_dojk_2018.pdf.
46. Kahl KL. Association between pCR and neoadjuvant chemo shows improved breast cancer outcomes. San Antonio Breast Cancer Symposium. 2018 Dec 6th; San Antonio: OncLIve; 2018 [cited 2019 Sep 23]. Available from: https://www.onclive.com/view/association-between-pcr-and-neoadjuvant-chemo-shows-improved-breast-cancer-outcomes.
47. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376(22):2147-59. DOI: 10.1056/NEJMoa1612645 PMID: 28564564
48. Goodman A. Role of Adjuvant Capecitabine in Triple-Negative Breast Cancer. Huntington: Harborside; 2019 [cited 2019 Sep 3]. Available from: https://www.ascopost.com/issues/january-25-2019/role-of-adjuvant-capecitabine-in-triple-negative-breast-cancer/.
49. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377(6):523-33. DOI: 10.1056/NEJMoa1706450 PMID: 28578601

50. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379(8):753-63. DOI: 10.1056/NEJMoa1802905 PMID: 30110579

51. Gavidia M. Phase 3 EMBRACA Findings Suggest No Overall Survival Benefit With Talazoparib in Advanced BRCA-Mutated Breast Cancer. AJMC American Journal of Managed CAre. 2020;26. [cited 2020 Sep 3]. Available from: https://www.ajmc.com/view/phase-3-embraca-findings-suggest-no-overall-survival-benefit-with-talazoparib-in-advanced-brcamutated-breast-cancer.

52. Wei R, Guo L, Wang Q, Miao J, Kwok HF, Lin Y. Targeting PD-L1 protein: translation, modification and transport. Curr Protein Pept Sci. 2019;20(1):82-91. DOI: 10.2174/1389203719666180928105632 PMID: 30264678

53. Udall M, Rizzo M, Kenny J, Doherty J, Dahm S, Robbins P, et al. PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. Diagn Pathol. 2018;13(1):12. DOI: 10.1186/s13000-018-0689-9 PMID: 29426340

54. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al.; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advance triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-21. DOI: 10.1056/NEJMoa1809615 PMID: 30345906

55. Khan MA, Jain VK, Rizwanullah M, Ahmad J, Jain K. PI3K/AKT/mTOR pathway inhibitors in triple-negative breast cancer: a review on drug discovery and future challenges. Drug Discov Today. 2019;24(11):2181-91. DOI: 10.1016/j.drudis.2019.09.001 PMID: 31520748