RESEARCH ARTICLE

Body mass index as a prognostic factor in HER-2 positive early breast cancer patients and its effect on duration of treatment with Trastuzumab: A retrospective study

Samaa AbdAlla Bardisi[1], Amany Mostafa ElFeky[2], Eman Ismail Ibrahim[3], Yousra Dorgham[4], Emad Abd Elmongy Sadaka[5]

Abstract

Objective: To evaluate prognostic value of body mass index in human epidermal growth factor receptor 2-positive early breast cancer, and to evaluate the duration of trastuzumab administration.

Methods: The retrospective study was conducted from March 2020 to December 2021 at Kafrelsheikh University Hospital and Zagazig University Hospital, Egypt, and comprised data of women diagnosed between 2015 and 2017 with stage I-II human epidermal growth factor receptor 2-positivebreast cancer, who were treated with adjuvant chemotherapy and trastuzumab for a year. Body mass index had been calculated at the time of diagnosis, and data was divided into 3 groups: average weight group A, overweight group B and obese group C. Disease-free survival, distant disease-free survival and overall survival were estimated for all the three groups. Data was analysed using SPSS 26.

Results: The mean age of 160 cases was 44.99±11.35 years (range: 25-66 years). There were 93(58.1) postmenopausal women, 60(37.5%) had positive family history and 128 (80%) underwent modified radical mastectomy. There were 60(37.5%) patients in group A, 49(30.6%) in group B and 51(31.9%) in group C. There was significant association of body mass index with disease-free survival and distant disease-free survival ($p<0.05$), but not with overall survival ($p>0.05$). Significant difference was noted between body mass index and duration of trastuzumab ($p<0.001$).

Conclusion: Body mass index was found to be an independent prognostic factor for human epidermal growth factor receptor 2-positiveearly breast cancer.

Keywords: Prognosis, Breast neoplasms, Trastuzumab, Chemotherapy, Adjuvant, Obesity.

DOI: 10.47391/JPMA.EGY-S4-51

Introduction

Breast cancer (BC) is an important health subject among women due to its high morbidity and mortality rate.[1]It is the most commonly diagnosed cancer.[2] BC is a heterogeneous disease showing many different biological and morphological features and entails different clinical behaviours and responses to treatment.[3]

Human epidermal growth factor receptor 2-positive (HER2+) BC represents approximately 15-20% of all BC cases. This subtype was linked to a higher risk of occurrence of systemic and brain metastases and worse overall survival (OS).[4]HER2+ malignancies <2cm in diameter provided a 20-30% risk for distance metastases.[5]HER2+ BC typically returns in visceral locations as opposed to luminal subtypes.[6]

[1,2,5]Department of Clinical Oncology and Nuclear Medicine, Kafrelsheikh University, Egypt.

[3,4]Department of Clinical Oncology and Nuclear Medicine, Zagazig University, Egypt.

Corrospondience: Samaa AbdAlla Bardisi

email: samaabardisi77@gmail.com

The emergence of anti-HER2 medications undoubtedly improved the clinical prognosis in individuals with HER2+ BC. Trastuzumab (TTZ) with chemotherapy reduces relative risk (RR) by about 40% and death by 34%.[7]But some HER2+ BC patients experience poor outcomes despite receiving most effective anti-HER2 therapies.[8]

One year remains the standard duration of TTZ. Recently, a meta-analysis of 12-month versus shorter therapy adopted a non-inferiority design.[9]

After BC diagnosis, the immediate challenge is to determine prognosis and to identify the most suitable adjuvant systemic therapy.[10]

HER2+ early BC (eBC)itself is a biologically heterogeneous disease. Its outcome is influenced by both tumour biology and host factors, including obesity and body mass index (BMI). BC patients who are obese have worse prognosis because they are less likely to undergo screening and the disease is discovered at an advanced stage, increasing operating time and complications post-surgery, and sub-optimal chemotherapy treatment.[2]Also, in obese patients it is more difficult to detect primary tumour and enlarged axillary lymph node (LN). According to a study analysing the mapping of axillary LNs,BMI had an adverse effect on

the procedure which failed in individuals with increased mean BMI.[11]

Epidemiological data suggests that obesity is an independent risk factor for many solid tumours, including BC[12], in addition to worse quality of life (QOL) and increased risk of having lymphoedema and comorbidities, such as hypertension (HTN), diabetes mellitus (DM) and cardiovascular disease (CVD).[13]

Numerous studies have shown that HER2+ BC is a lipogenic illness where bio-energetic preservation of HER2+ BC and resistance to anti-HER2 target therapy are strongly influenced by fatty acid de novo production and Fatty Acid (FA) absorption.[8]

The connection between patient adiposity/BMI and clinical results in patients with HER2+ BC could be explained by a number of mechanisms, like insulin receptor and the insulin-like growth factor 1 (IGF-1)[14], leptin and adiponectin[15], TTZ pharmacokinetics[8], sex hormone alternation[14], adipose chronic inflammation[13], and lipid metabolism.[8] IGF-1 is a hormone that increases with hyperinsulinaemia related to obesity and activates the Mitogen-Activated Protein Kinase (MAPK) and Phosphatidylinositol-3-Kinase (PI3K) pathways, causing cancer-promoting effects of obesity, and reveals mitogenic and anti-apoptotic effects. Increased insulin and IGF-1 levels are associated with increased mortality and poor survival outcomes in BC cases.[14]

The most important factor for obesity linked to BC is leptin which promotes tumour initiation, development, growth and metastasis, and causes cross-talk with other signalling molecules.[15]Leptin receptor can increase HER2 protein levels and it can transactivate oestrogen receptor (ER).[8]Due to the negative relationship between patient BMI and TTZ plasma levels, obesity can influence the pharmacokinetics of anti-HER2 medicines.[8]

Oestrogen, which is created by aromatase conversion of androgens, may contribute to cancer via impacting signalling pathways that result in deoxyribonucleic acid (DNA) damage, activation of angiogenesis, mutagenesis and cell proliferation.[14]

Obesity is characterised by a chronic low-grade inflammation. Tumor Necrosis Factor-Alpha (TNF-□), Monocyte chemoattractant protein-1(MCP-1), interleukin-6 (IL-6) and Cyclooxygenase-2 (COX-2) are examples of the pro-inflammatory mediators highly produced from activated macrophages in the adipose tissue that promote tumour progression.[13] Also, chronic inflammation in the adipose tissue promotes cancer growth and encourages angiogenesis.[14]

Regulating the development and proliferation of HER2+ BC cells, and treatment resistance are associated with plasmatic lipid uptake. Therefore, the fate of HER2+ BC patients may be affected by elevated circulating lipid contents.[8]

BMI, according to the World Health Organisation (WHO), is a statistical index determined by dividing a person's weight in kilogrammes by their height in metres squared: BMI = weight (in kg)/ height^2 (in m^2). Obesity is defined as BMI >30kg/m^2 and overweight as a BMI >25kg/m^2.[16]

Currently, >1.9 billion and >600 million individuals can be classified as overweight and obese, respectively, and the numbers will keep rising in the coming years.[17]

Studies examining the relationship between obesity and HER2+ eBC prognosis have reported mixed findings.[18] Despite the abundance of research on the link between BMI and BC, there is a lack of information regarding patient, tumour and therapy factors that may affect this association and outcome.[19]

The current study was planned to evaluate prognostic value of BMI in HER2-positive-BC cases, and to evaluate the duration of TTZ administration.

Patients and Methods

The retrospective study was conducted from March 2020 to December 2021 at Kafrelsheikh University Hospital and Zagazig University Hospital, Egypt, and comprised data of women diagnosed between 2015 and 2017 with histopathologically proven stage I-II HER2+ invasive eBC, who finished adjuvant chemotherapy and received TTZ for a year. Data was retrieved using convenience sampling technique after approval from the ethics review committee of Kafrelsheikh University Hospital. Data was excluded if it was related to patients with advanced or metastatic BC, HER2-negative type and BC of non-epithelial origin, such as phyllodes tumour, sarcoma, or lymphoma.

HER-2 positivity was defined as score +3 by immunohistochemistry (IHC) in more than 10% of immune-reactive cells, or amplification of erythroblastic oncogene B (ERBB2) by in situ hybridisation.

All patients had been subjected to accurate diagnosis and proper staging. Personal history included age, menopausal status and marital status, while present history included symptoms and duration, and past history included medical comorbidities and their treatments, family history including cancer history, date of surgery and modality of treatment, including surgical procedure, supplementary radiation, adjuvant chemotherapy and hormonal therapy.

Laboratory investigations included complete blood count (CBC) with total and differential count, liver function tests (LFTs) and renal function tests (RFTs).

Radiological investigations included mammography and ultrasound (US) of breast and axilla, where available, plain chest X-ray (CXR) and computed tomography (CT), when needed, pelvi-abdominal US and/or CT scan, bone scan, if indicated, and echocardiography with special emphasis on left ventricular ejection fraction (LVEF).

Histopathological data included size of tumour, LN status, histopathological type, pathological stage according to the American Joint Committee on Cancer (AJCC)staging guideline [20], grade and presence of ductal carcinoma in situ (DCIS), lymph vascular invasion (LVI) or central necrosis. IHC examination done on tumour specimens imbedded in paraffin blocks included ER, progesterone receptor (PR), HER2and Kiel-67 (Ki-67). HER2 status was examined by IHC or fluorescence in-situ-hyperdisation(FISH). HER2+ was shown by the overexpression of the HER2 gene which had an IHC score of 3+ and scores of 0 and 1+ suggestedHER2 negativity, while score 2+ was considered equivocal, which was confirmed through FISH. A HER2/CEP17 (Centromeric Region Of Chromosome 17) ratio of 2.0 or higher, or a copy number of the HER2 gene of 6 or more on FISH suggested overexpression of the HER2 gene.

The patients received TTZ intravenous (IV) infusion once every 21days, with 8mg/kg as the loading dose, followed by maintenance dose of 6mg/kg for one year, according to a clinical trial done in 2005. [21]

BMI had been calculated at the time of diagnosis, and data was divided into 3 groups: average weight group A, overweight group B and obese group C. There was an insignificant number of underweight patients and their data was made part of group A. Disease-free survival (DFS), distant disease-free survival (DDFS) and OS were estimated for all the three groups.

Data was analysed using SPSS 26. Quantitative data was presented as mean ± standard deviation, and qualitative data as frequencies and percentages. One-way analysis of variance (ANOVA) test was used to compare more than two groups of normally distributed variables. Paired sample t-test was used to compare between pre- and post-treatment results of normally distributed variables. Categorical variables were compared using Chi-square test. Kaplan-Meier method was used for survival assessment. Hazard ratio (HR) and associated 95% confidence interval (CI) of any recurrence were determined using Cox multivariate proportional hazard regression model. P<0.05 was considered statistically significant.

Results

The mean age of 160 cases was 44.99±11.35 years (range: 25-66 years), and mean BMI was 28.43±6.01kg/m^2 (range: 17-46.6kg/m^2). There were 60(37.5%) patients in group A, 49(30.6%) in group B and 51(31.9%) in group C. Overall, there were 93(58.1) postmenopausal women, 60(37.5%) had positive family history and 128 (80%) underwent modified radical mastectomy (MRM). Regarding tumour characteristics, 102(63.8%) cases were of stage T2 and 93(58.1%) were N+, 160(100%) are M0and 149(93.1%) were stage II (Table 1). The median (IQR) follow-up was 68.0 months (64.0-71.0)

The relationship between BMI and DFS was significant, and the highest mean duration was in group A (p<0.001). The finding was confirmed by Kaplan Meier analysis (Figure)as well as by multivariate analysis (*p*=0.01) (Table 2). Group B patients had no significant difference compared to group A patients (*p*>0.05).

Significant difference was noted between BMI and DDFS, and the lowest mean duration was in group C patients (*p*= 0.007). The impact of obesity was significant in post-menopausal obese patients (*p*=0.017), but was of no significance in pre-menopausal patients (*p*>0.05).

No significant difference was found between BMI and OS (*p*=0.1).

The mean DFS duration was 62.16±10.41 months and the mean OS duration was 64.89±7.03 months (Table 3).

There was significant difference between BMI and TTZ duration, and the highest mean duration was in group C cases (*p*<0.001) (Table 4). Also, there was significant difference between BMI and number of dissected LNs, where the lowest mean number was in group A patients (*p*<0.05).

Table-1: Demographicand tumour characteristics(n=160)

Characteristic	Category	Cases group N=160 n (%)
Age (years)	Mean ±SD	44.99±11.35
	(min-max)	(25-66)
BMI	Mean ±SD	28.43±6.01
	(min-max)	(17-46.6)
BMI	Average weight (18 - <25)	60 (37.5)
	Overweight (25 - <30)	49 (30.6)
	Obese ≥30	51 (31.9)
Family history	Negative	100 (62.3)
	Positive	60 (37.5)
Menstruation	Premenopausal	67 (41.9)
	Postmenopausal	93 (58.1)

Continued on next page

Table-1: *continued from previous page*

Characteristic	Category	Cases group N=160 n (%)
Lymph node dissected	Mean ±SD	17.15±7.35
	(min-max)	(7-27)
T stage	T1	34 (21.3)
	T2	102 (63.8)
	T3	24 (15)
N stage	N0	67 (41.9)
	N1	93 (58.1)
AJCC stage group	Stage I	11 (6.9)
	Stage II	149 (93.1)
ER	Negative	61 (38.1)
	Positive	99 (61.9)
PR	Negative	73 (45.6)
	Positive	87 (54.4)
HER2	IHC +ve	104 (65)
	FISH +ve	56 (35)
Ki-67	Low (<20)	93 (58.1)
	High (>20)	67 (41.9)
Molecular Subtype	Luminal B	99 (61.9)
	HER2 enriched	61 (38.1)

BMI: Body mass index, **AJCC:** American Joint Committee on Cancer, **ER:** Oestrogen receptor, **PR:** Progesterone receptor, **HER2:** Human epidermal growth factor receptor 2. **IHC:** Immuno-histochemistry, **FISH:** Fluorescence insitu-hyperdisation, Ki-67: Kiel-67, **SD:** Standard deviation.

Table-2: Cox regression analysis of DFS and OS in relation to BMI(n=160).

Variable	Category according to BMI	Hazard ratio	95% confidence interval		*p-value*
			Lower bond	Upper bond	
DFS	average weight (n=60)	Reference			
	Overweight (N=49)	1.044	.248	4.391	0.953
	Obese (n=51)	6.093	1.550	23.958	0.01*
OS	average weight (n=60)	Reference			
	Overweight (N=49)	1.178	.281	4.937	0.832
	Obese (n=51)	3.121	.805	12.098	0.1

BMI: Body mass index, DFS: Disease-free survival, **OS:** Overall survival.
*: Statistically significant at $p \leq 0.05$

Table-3: Disease-free survival (DFS) and overall survival (OS) duration(n=160).

Variables	Study group (n=160)
DFS duration	
Mean ±SD	62.16±10.41
Range	(36-80)
OS Duration	
Mean ±SD	64.89±7.03
Range	(47-80)

SD: Standard deviation/

Table-4: Body mass index (BMI) and herceptin duration(n=160)

Characteristic	Average weight (<25) N=60	Overweight (25 - <30) N=49	Obese ≥30 N=51	f	*p-value*	Post hoc
Herceptin duration						
Mean ±SD	13.75±0.77	14.18±0.95	14.88±1.03	21.190	<0.001*	P1=0.015
						P2<0.001*
						P3<0.001*

*: Statistically significant at $p \leq 0.05$

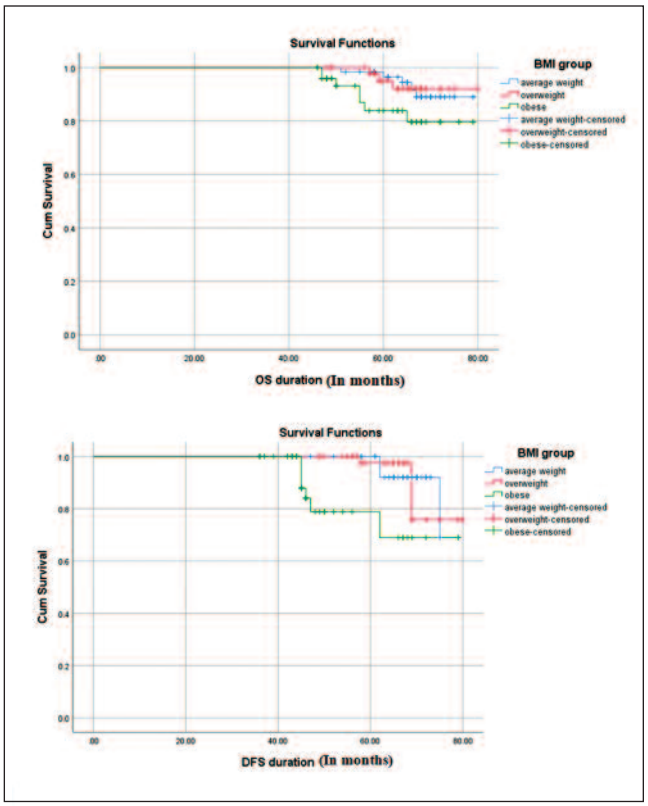

Figure: Kaplan-Meier for survival time of OS and DFS(n=160).
BMI: Body mass index, DFS: Disease-free survival, OS: Overall survival.

Discussion

BC affects one in 8 women, almost 25.4% of all new cancer cases in women.[2]HER2 status is an important prognostic marker that has an aggressive behaviour to HER2+ BCtumours.[22]

Studies examining the impact of obesity on BC survival have produced conflicting results.[18,19,23,24]The impact of obesity in the HER2+ population is not fully understood, particularly in the wake of the advent of adjuvant TTZ.[24]

The median follow-up in the current study was 68 months, as previous studies have shown that the risk of recurrence in eBC peaks in the first 2-3 years, then continuously declines from 3-5years, after which it declines far more

slowly. Additionally, earlier survival analyses with longer follow-ups has demonstrated that the primary advantage of HER2-target therapy is a decrease in early recurrence.[24]

IN line with the current findings, Ligorio et al. showed that obese patients with HR-/HER2+ subtype had worse DFS and OS compared to those with low BMI.[8] Sun. et al. found that being overweight and being obese were separate risk factors for mortality and 5-year BC relapse.[23]Cantini et al. showed no significant differences between BMI classes and prognosis in the total population of HER2+ malignancies.[24]

As regard nodal status, the current findings were consistent with Keskin O. et al[11]., but BMI and the number of metastatic LNs did not correlate significantly, and the mean number of the dissected and involved LNs was larger in the HER2+ group compared to the negative ones.[11]

The current findings related to TTZ and allied treatment were in agreement with Ligorio et al.[8]but in contrast with Martel et al. whose patients received chemotherapy and different anti-HER2 therapies including lapatinib, TTZ, TTZ followed by lapatinib or TTZ + lapatinib.[18]

As regard TTZ duration, all current patients received TTZ for 1 year, and the association was significant between BMI and Herceptin duration, where the highest mean duration was among obese cases. This relatively longer duration may be related to other factors rather than obesity, or any interruption of the treatment.

According to Cantini et al., escalation techniques that involve supplementing regular TTZ with additional anti-HER2 medications may be advantageous for patients with HR-/BMI≥25, whereas people with HR+/BMI<25 may be suited for shorter TTZ therapy.[24]

As for menopausal status, the current study found significant differences between BMI and menopausal status, where most postmenopausal cases (80.4%) were obese and the negative impact of obesity was significantly correlated with postmenopausal status.

This was in agreement with Lohmann, A. et al. who showed that following a 6-year follow-up, obese postmenopausal women had a higher probability of dying from BC than normal-weight women.[25]Sun, L. et al. discovered that obesity at the time of diagnosis was associated with a bad prognosis for BC regardless of the menopausal status, whereas being overweight was associated with prognosis in postmenopausal women.[23]

With respect to the hormonal status, 61.9% of current cases were HR+, and there was significant difference between BMI and hormonal status(p=0.019). But one examination of the effect of hormonal status on survival in obese patients, there was no association of hormonal status with DFS, OS and DDFS. The findings were in line with Martel et al. even though their patients received different anti-HER2 therapy in the adjuvant setting.[18]

The current study has its limitations, including its retrospective design and its relatively small sample size which was not statistically calculated. Also, the sample was raised using convenience sampling. As weight change may affect prognosis, it is recommended that future prospective, large-scale studies should measure BMI multiple times and calculate weight change during treatment and follow-up.

Conclusion

BMI was found to be an independent prognostic factor for HER2+eBC cases. Obesity may interrupt ideal treatment, and may prolong duration of TTZ treatment.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures. Biomed Res Int 2022;2022:e9605439. doi: 10.1155/2022/9605439.
2. Crafts TD, Tonneson JE, Wolfe BM, Stroud AM. Obesity and breast cancer: Preventive and therapeutic possibilities for bariatric surgery. Obesity (Silver Spring) 2022;30:587-98. doi: 10.1002/oby.23369.
3. Tsang JYS, Tse GM. Molecular Classification of Breast Cancer. Adv Anat Pathol 2020;27:27-35. doi: 10.1097/PAP.0000000000000232.
4. Exman P, Tolaney SM. HER2-positive metastatic breast cancer: a comprehensive review. Clin Adv Hematol Oncol 2021;19:40-50.
5. Joensuu H. Escalating and de-escalating treatment in HER2-positive early breast cancer. Cancer Treat Rev 2017;52:1-11. doi: 10.1016/j.ctrv.2016.11.002.
6. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Gelmon K. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010;28:3271-7. doi: 10.1200/JCO.2009.25.9820.
7. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev 2012;2012(4):CD006243. doi: 10.1002/14651858.CD006243.pub2.
8. Ligorio F, Zambelli L, Fucà G, Lobefaro R, Santamaria M, Zattarin E, et al. Prognostic impact of body mass index (BMI) in HER2+ breast cancer treated with anti-HER2 therapies: from preclinical rationale to clinical implications. Ther Adv Med Oncol 2022;14:e17588359221079123. doi: 10.1177/17588359221079123.
9. Thomssen C, Fehm TN, Stickeler E, Fasching PA, Janni W, Kolberg-Liedtke C, et al. Update Breast Cancer 2021 Part 4 - Prevention and Early Stages. Geburtshilfe Frauenheilkd 2022;82:206-14. doi: 10.1055/a-1724-9639.
10. Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: Past, present and future. Semin Cancer Biol 2018;52:56-73. doi: 10.1016/j.semcancer.2017.08.010.

11. Keskin O, Aksoy S, Babacan T, Sarici F, Kertmen N, Solak M, et al. Impact of the obesity on lymph node status in operable breast cancer patients. J BUON 2013;18:824-30.
12. Di Cosimo S, Porcu L, Agbor-Tarh D, Cinieri S, Franzoi MA, De Santis MC, et al. Effect of body mass index on response to neo-adjuvant therapy in HER2-positive breast cancer: an exploratory analysis of the NeoALTTO trial. Breast Cancer Res 2020;22:115. doi: 10.1186/s13058-020-01356-w.
13. Chan S, Chen JH, Li S, Chang R, Yeh DC, Chang RF, et al. Evaluation of the association between quantitative mammographic density and breast cancer occurred in different quadrants. BMC Cancer 2017;17:274. doi: 10.1186/s12885-017-3270-0.
14. Atoum MF, Alzoughool F, Al-Hourani H. Linkage Between Obesity Leptin and Breast Cancer. Breast Cancer (Auckl) 2020;14:e 1178223419898458. doi: 10.1177/1178223419898458.
15. Barone I, Giordano C, Bonofiglio D, Andò S, Catalano S. Leptin, obesity and breast cancer: progress to understanding the molecular connections. Curr Opin Pharmacol 2016;31:83-9. doi: 10.1016/j.coph.2016.10.003
16. World Health Organization (WHO). Obesity and overweight. News release. The WHO Media Centre. [Online] 2021 [Cited 2022 November 24]. Available from URL: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
17. Barone I, Giordano C, Bonofiglio D, Andò S, Catalano S. The weight of obesity in breast cancer progression and metastasis: Clinical and molecular perspectives. Semin Cancer Biol 2020;60:274-84. doi: 10.1016/j.semcancer.2019.09.001
18. Martel S, Lambertini M, Agbor-Tarh D, Ponde NF, Gombos A, Paterson V, et al. Body Mass Index and Weight Change in Patients With HER2-Positive Early Breast Cancer: Exploratory Analysis of the ALTTO BIG 2-06 Trial. J Natl Compr Canc Netw 2021;19:181-9. doi: 10.6004/jnccn.2020.7606.
19. Cecchini RS, Swain SM, Costantino JP, Rastogi P, Jeong JH, Anderson SJ, et al. Body Mass Index at Diagnosis and Breast Cancer Survival Prognosis in Clinical Trial Populations from NRG Oncology/NSABP B-30, B-31, B-34, and B-38. Cancer Epidemiol Biomarkers Prev 2016;25:51-9. doi: 10.1158/1055-9965.EPI-15-0334-T.
20. American College of Surgeons. In: Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al, eds. AJCC Cancer Staging Manual, 8th ed. Chicago, USA: Springer International Publishing AG; 2017.
21. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72. doi: 10.1056/NEJMoa052306.
22. Martel S, Poletto E, Ferreira AR, Lambertini M, Sottotetti F, Bertolini I, et al. Impact of body mass index on the clinical outcomes of patients with HER2-positive metastatic breast cancer. Breast 2018;37:142-7. doi: 10.1016/j.breast.2017.11.004.
23. Sun L, Zhu Y, Qian Q, Tang L. Body mass index and prognosis of breast cancer: An analysis by menstruation status when breast cancer diagnosis. Medicine (Baltimore) 2018;97:e11220. doi: 10.1097/MD.0000000000011220.
24. Cantini L, Pistelli M, Merloni F, Fontana A, Bertolini I, De Angelis C, et al. Body Mass Index and Hormone Receptor Status Influence Recurrence Risk in HER2-Positive Early Breast Cancer Patients. Clin Breast Cancer 2020;20:e89-e98. doi: 10.1016/j.clbc.2019.06.008.
25. Lohmann AE, Soldera SV, Pimentel I, Ribnikar D, Ennis M, Amir E, et al. Association of Obesity With Breast Cancer Outcome in Relation to Cancer Subtypes: A Meta-Analysis. J Natl Cancer Inst 2021;113:1465-75. doi: 10.1093/jnci/djab023.