

Evaluation of Prognostic Factors in Invasive Breast Cancer Patients Receiving Adjuvant Radiotherapy

Adjuvan Radyoterapi Alan İnvaziv Meme Kanseri Hastalarında Prognostik Faktörlerin Değerlendirilmesi

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Özet

Amaç: Bu çalışmanın amacı, invaziv meme kanserli hastalara uygulanan adjuvan radyoterapinin sağkalıma etkisini araştırmak ve hastaların prognostik faktörleri ile sağkalım arasındaki ilişkiyi belirlemektir.

Giriş: Yaşları 35-55 yaş arası olan kadınlarda meme kanseri en sık ölüm nedenidir. Meme kanserlerinde cerrahi, kemoradyoterapi, radyoterapi, hormon tedavisi ve immünoterapi uygulanan tedavi yöntemleridir.

Gereç ve Yöntemler: Mayıs 2016-Mart 2019 tarihleri arasında Adana Şehir Eğitim ve Araştırma Hastanesi Radyasyon Onkolojisi polikliniğine başvuran ve invaziv meme kanseri nedeniyle adjuvan radyoterapi alan, yaşları 39-68 arasında olan 120 hasta, retrospektif olarak çalışmamıza dahil edildi.

Bulgular: Lenfovasküler invazyon, insan epidermal büyüme faktörü reseptör 2 pozitifliği, tümör ve lenf nodu durumu ile genel sağkalım arasında istatistiksel olarak anlamlı bulgular elde edildi. Fakat menapoz durumu, uygulanan cerrahi yöntem, histopatolojik tümör tipi, ekstrakapsüler invazyon varlığı, östrojen ve progesteron hormon reseptörleri ile genel sağkalım arasında istatistiksel olarak anlamlı bir bulguya ulaşılmadı. Östrojen ve progesteron reseptörlerinin pozitif olması prognoz açısından olumlu bulunurken, Her2 pozitif olması prognoz açısından olumsuz bulunmuştur.

Tartışma: Çalışmaya dahil edilen hasta sayısının yetersiz olmasından dolayı, istatistiki olarak anlamsız sonuçlar elde ettiğimizi düşünmemize rağmen bu sonuçların genel sağkalım üzerindeki etkilerini gösterdik. Modern görüntüleme yöntemleriyle erken teşhis, meme kanserinde genel sağkalımı artırır da, uygun hastalar için uygun tedavilerin seçimi çok önemlidir.

Sonuç: İstatistiksel olarak yeterince belirleyemsek de, literatürdeki önceki çalışmalar ve bu çalışmada ki gözlemlerimiz ışığında adjuvan radyoterapinin sağkalımı olumlu etkilediği sonucuna vardık.

Anahtar Kelimeler: İnvazif meme kanseri, Radyoterapi, Prognostik faktörler

Abstract

Objective: The aim of this study is to investigate the effect of adjuvant radiotherapy applied on patients with invasive breast cancer on survival and to determine the relationship between prognostic factors and survival in patients.

Introduction: Breast cancer is the most common cause of death in women between the ages of 35-55. Surgery, chemoradiotherapy, radiotherapy, hormone therapy and immunotherapy are treatment modalities applied in breast cancers.

Materials and Methods: Our retrospective study included 120 patients ranging between 39 and 68 years who were admitted to Adana City Education and Research Hospital Radiation Oncology outpatient clinic between May 2016 and March 2019 and who received adjuvant radiotherapy due to invasive breast cancer.

Results: Statistically significant findings were obtained between lymphovascular invasion, human epidermal growth factor receptor 2 positivity, tumor and lymph node status and overall survival. But, no statistically significant findings could be attained between menopause status, surgical method applied, histopathological type of tumor, presence of extracapsular invasion, estrogen and progesterone hormone receptors and overall survival. While estrogen and progesterone receptors were found to be positive in terms of prognosis, Her2 positive was found to be negative in terms of prognosis.

Discussion: Statistically insignificant results are thought to arise from insufficient number of patients incorporated in the study, however, their effect on overall survival was exhibited. Although early diagnosis with modern imaging methods increases overall survival in breast cancer, the selection of appropriate treatments for suitable patients is crucial.

Conclusion: Even though we could not specify enough statistically, we concluded that adjuvant radiotherapy positively affected survival in the light of previous studies in the literature and our observations during present study.

Key Words: Invasive breast cancer, Radiotherapy, Prognostic factors

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INTRODUCTION

Breast cancer (BC), is the most common cause of death in women between the ages of 35-55. Although it is the most common neoplasm in women, it is seen infrequent in men. The overall survival (OS) rate varies according to the stage of BC and five-year OS for all BC patients is approximately 65%. Various prognostic factors have been identified, such as tumor type, size and histology, axillary lymph node involvement, vascular invasion and hormone receptor status (1,2). Lymph node status is the most significant of all these prognostic factors. In the United States, the 5-year OS was 92% in patients without lymph node involvement, 81% in patients with one to three axillary lymph nodes involvement and 57% in those with more than four involved nodes (3).

Previous studies indicated that adjuvant radiotherapy (aRT) for BC is effective on locoregional control but it doesn't contribute on OS. Entity of undiagnosed micrometastases of BCs is thought as a reason of inefficacy of aRT. Acknowledged studies demonstrates concealed micrometastases of BCs are associated with locoregional control as well as the prognosis (4,5). Therefore, evaluation of micrometastases of BCs is substantial for estimating the prognosis of the disease.

In recent past, aRT was the essential treatment method for the high risk premenopausal women by itself (6), however, it has been abandoned due to its inefficacy on OS (7). Subsequent clinical trials exhibited that adjuvant chemotherapy (aCT) and hormonal therapies increased the OS, therefore, one or both of these methods were started to be applied on BC patients (8,9). Moreover, many studies about the early stage of BC specified that RT following breast conserving surgery (BCS) has the same efficacy with modified radical mastectomy (MRM) on OS (10,11). As a consequence CT, RT and hormonal therapy are utilized after BCS. Despite BCS is adopted by surgeons generally, MRM still remains a surgical option for locally diffuse BCs. Although in recent past clinical trials demonstrated aRT contributes on local control on BC but ineffective on OS (12), following studies indicated both use of aCT and aRT reduced mortality in premenopausal BC patients with positive lymph node owing to their effect of locoregional and systemic relapse (13).

On the other hand, another study denoted aRT following MRM was significantly effective on increasing OS in patients with high risk BC (14). Thanks to advancing technology, aRT has gained widespread use in the world. The aim of this study is to investigate the effect of adjuvant RT applied on patients with invasive BC on survival and to determine the relationship between prognostic factors and survival in patients.

MATERIALS AND METHODS

The study included 120 patients ranging between 39 and 68 years who were admitted to Adana City Education and Research Hospital Radiation Oncology outpatient clinic between May 2016 and March 2019 and who received aRT due to invasive BC. The study was conducted retrospectively after obtaining the ethics committee approval from the

Cukurova University Faculty of Medicine Ethics Committee (Date: 05.04.2019, Session No: 87, Decision No: 68).

Radiotherapy management

Patients undergoing BCS were given 50 Gy to all breast and 10 Gy to the tumor bed with a total dose of 60 Gy external RT by Intensity Modulated Radiotherapy (IMRT) method. Depending on the involvement of the lymph nodes, 50 Gy external curative RT was applied to the relevant lymph nodes by IMRT method.

Patients with MRM were given 50 Gy external curative RT to the surgical site. Depending on the involvement of the lymph nodes, 50 Gy external curative RT was given to the suitable lymph nodes regions by IMRT method.

Statistical analysis

Descriptive statistics for the continuous variables were presented as Mean, Standard deviation; minimum and maximum values while count and percentages for categorical variables. Chi-square analysis was performed to determine risk factors for Survival status (Exitus or live). In addition Odds ratio of the risk factors was computed for the survival status. Statistical significance level was considered as 5% and SPSS (ver: 20) statistical program was used for all statistical computations.

RESULTS

Three of the patients were male (2.5%) and 117 (97.5%) were female. According to histopathological type, 98 (81.6%) of the patients were invasive ductal carcinoma, 20 (16.6%) were invasive lobular carcinoma, 2 (1.6%) were mixed carcinoma (**Table 1**). All male patients had invasive Ductal carcinoma pathology. External RT was given to the patients curatively. When the axillary lymph node dissection of the patients was examined, it was found to be 13.99 (3.27). Positive lymph node number was 3.83 (0.12). Disease-free survival was found as 25.53 (18-30) months.

In control examinations, 8 patients (6.7%) had only bone metastasis, another 8 patients (6.7%) had bone and brain metastases simultaneously and 104 (86.7%) patients were followed without metastases. 24 (20%) of the patients were performed BCS and 96 (80%) of MRM. In addition, 43 (36.7%) of the female patients were diagnosed in premenopausal period, 74 (63.3%) in the postmenopausal period.

In the staging, "American Joint Committee on Cancer" (AJCC) 7th edition tumor, nodes metastasis (TNM) system was used (15).

51 (42.5%) grade-1, 56 (46.7%) grade-2, 13 (10.8%) grade-3 patients were included in the study and the relationship between histopathological grade and survival was not statistically significant in the table showing the risk prediction according to histopathological grade ($p=0.487$) (**Table 2**).

A statistically significant result was achieved between the increase of T ($p=0.004$) and N ($p=0.001$) and the mortality of the patients. While the stage at the time of diagnosis increases in breast cancer, its survival decreases ($p=0.001$) (**Table 3**).

Table 1. Table showing the pathological characteristics and prognostic factors of the patients

T _p size	N (%)	Pathological type	N (%)
T1	27 (22.5)	Ductal	98 (81.6)
T2	69 (57.5)	Lobular	20 (16.7)
T3	24 (20.0)	Mix	2 (1.6)
N _p		Herceptin receptor	
N0	30 (25.0)	Positive	62 (51.7)
N1	36 (30.0)	Negative	58 (48.3)
N2	43 (35.8)	Triple negative (Basal like)	15 (12.5)
N3	11 (9.2)	Her2neu+=ER/PR – Her2neu +	6 (5)
E		Extracapsular invasion	
1A	11 (9.2)	Positive	22 (18.3)
1B	7 (5.8)	Negative	98 (81.7)
2A	14 (11.7)	Grade	
2B	35 (29.2)	1	51 (42.5)
3A	43 (35.8)	2	56 (46.7)
3C	10 (8.3)	3	13 (10.8)
Estrogen receptor		Progesterone receptor	
Positive	90 (75.0)	Positive	93 (77.5)
Negative	30 (25.0)	Negative	27 (22.5)
Lymphovascular invasion		Patients status	
Positive	38 (31.7)	Exitus	8 (6.7)
Negative	82 (68.3)	Alive	112(93.3)

Table 2. Histological grade related distribution of alive and exitus patients

Grade	Total	Exitus	Alive	P
	N (%)	N (%)	N (%)	
1	51 (42.5)	3 (37.5)	48 (42.9)	0.487
2	56 (46.7)	5 (67.5)	51 (45.5)	
3	13 (10.8)	0 (0)	13 (11.6)	

Table 3. T and N, stage related distribution of alive and exitus patients

	Exitus	Alive	P
	N (%)	N (%)	
T			
1	0 (0)	27 (100)	0.004
2	3 (4.3)	66 (95.7)	
3	5 (21.7)	18 (78.3)	
N			
0	1 (3.4)	29 (96.6)	0.001
1	1 (2.8)	35 (97.2)	
2	2 (4.7)	41(95.3)	
3	4 (36.4)	7 (63.6)	
Stage			
1A	0(0)	11(100)	0.001
1B	0(0)	7(100)	
2A	0(0)	14(100)	
2B	2(5.7)	33(94.3)	
3A	2(4.7)	41(95.3)	
3C	4(40)	6(60)	

The results of the analysis to determine the relationships between certain risk factors and survival are summarized in **Table 4**. Accordingly, despite no statistically significant relationship was found between the menopausal status and survival of patients, it was observed that the risk of exitus in the premenopausal period tended to be approximately 3 times higher (OR=3.333) than in the postmenopausal period. Similarly, although there was no statistically significant relationship between MRM or BCS practice and survival, the risk of exitus in MRM treated patients tended to be approximately 2 (OR=2.119) times higher than those treated with BCS. In addition, there was no statistically significant relationship between survival and extracapsular invasion (ECI) status, however, the risk of exitus in patients with ECI increased by approximately 3 (1/0.344=2.91) times compared to patients without ECI. There was no expressive relationship between estrogen (ER) and progesterone (PgR) receptor status and survival, however, it was observed that if both hormone receptors were negative, risk of exitus increased approximately 2 times. Moreover, the relationship between invasive ductal or invasive lobular histopathological type and survival was not statistically significant. However, it has been perceived that invasive lobular carcinomas tend to be approximately 3 times more likely to be exitus than invasive ductal carcinomas (**Table 4**).

In contrast, we obtained statistically significant results between both human epidermal growth factor receptor 2 (Her2) and lymphovascular invasion (LVI) entities and survival (p<0.05). In this case, the risk of mortality was observed approximately 8 (8.235) times more in Her2 positive patients

Table 4. Pathological characteristics and survival table according to surgery in patients with breast cancer

	Exitus N (%)	Alive N (%)	P-Chi Square	Odds Ratio
Menopausal Status				
Premenopausal	5 (11.9)	38 (88.1)	0.095	3.333
Postmenopausal	7 (3.9)	71 (96.1)		
Type of surgery				
MRM	8 (8.4)	87 (91.6)	0.141	2.119
BCS	1 (4.2)	23 (95.8)		
ECl				
Negative	5 (5.2)	92 (94.8)	0.151	0.344
Positive	3 (13.6)	19 (86.4)		
ER				
Negative	3 (10)	27 (90)	0.407	1.867
Positive	5 (5.6)	84(94.4)		
PgR				
Negative	3 (11.1)	24 (88.9)	0.300	2.175
Positive	5(6.9)	87(94.6)		
Triple negative	3(20)	12(80)	0.027	0.200
Her2				
Negative	1(12.5)	7 (87.5)	0.023	8.373
Positive	61 (54.5)	51 (45.5)		
LVI				
Negative	2 (2.5)	79 (97.5)	0.007	0.135
Positive	6 (15.8)	23 (84.2)		
Pathology				
Invasive ductal	5 (5.1)	93 (94.9)	0.109	0.305
Invasive lobular	3 (15)	17 (85)		

MRM: Modified radical mastectomy, BCS: Breast conserving surgery, ER: Estrogen receptor, LVI: Lymphovascular invasion, PgR: Progesterone receptor, ECl: Extracapsular invasion

than in Her2 negative ones. Similarly, the risk of mortality was found to be approximately 7 (1/0.153=7.41) times higher in patients with LVI than in those without (**Table 4**).

DISCUSSION

In many western countries, the rate of mortality from BC is lower due to the increased availability of early detection methods and treatment options for BC. However, among European women, BC still ranks second among cancer-related deaths (16-18). Mammography screening performed every two years resulted in a significant reduction in the mortality of BC in women aged 50-69 years (19).

Age, pathological T and N status, tumor grade and histopathologic features at the time of diagnosis, LVI, receptor status (ER, PgR, Her2) and applied treatment modalities (sur-

gery, CT, RT, hormone therapy, immunotherapy) are considered as prognostic factors in BC. Ozturk et al., uttered that young age, LVI, negativity of ER, and asset of local or systemic metastasis adversely affected BC patients (20). The stage of the disease at the time of diagnosis, the status of regional lymph nodes and the dimension of the primary tumor are the most important factors for prognosis (21,22). In parallel with these data, descriptive statistics about the prognostic factors are shown in **Table 1**.

It is found that there is a strong correlation between histological grade and prognosis and survival in BC in the literature. In the studies performed by Patey, Bloom, and Hopton et al., significant correlation was detected between the histological grade and the prognosis of the disease (23,24,25). These studies delivered that patients with grade 1 tumors had

better survival than patients with grade 2 and grade 3 tumors. However, incompatible with these results, Metzger-Filho O et al. stated that histological grade was an independent prognostic factor in their study (26). In the present study, no statistically significant results were found between histological grade and survival ($p=0.487$) (**Table 2**).

As the T status of the patients increased, OS decreased in the present study and this was statistically significant ($p=0.004$). Similarly, OS decreases and this was also statistically significant ($p=0.001$) (**Table 3**). Increased T and N status of BC patients is an important prognostic factor (27).

In the study by Ruth et al., it was found that the risk of mortality was increased threefold in patients with late BC diagnosis than the patients with early BC diagnosis. In the same study, tumor size >2.5 cm, positive surgical margin and negative PgR increase the risk of mortality in the first two years (28). In other studies, T and N status of patients is important in clinical prognostic factors (29).

Up to 45% of premenopausal patients were included in the study conducted by Ozmen V. with BC patients, and 58% of patients had locally advanced BC. It was concluded that the diagnosis of BC is delayed due to the more intense breast in premenopausal patients and this leads to locally advanced BC, causing poor prognosis (30). In our study, the effect of menopausal status on survival was not statistically significant, but the mortality rate of patients in the premenopausal period was approximately 3 times higher than in postmenopausal patients (**Table 4**).

Tasci et al. stated besides MRM, BCS is also a correct surgical approach in properly selected patients (31). They explicated that RT after MRM increases OS in patients with high risk BC, while RT after BCS has a similar effect (32-34). In our study, no statistically significant relationship was found between MRM or BCS practice and survival, but the risk of exitus was increased in patients who received MRM compared to those who received BCS (**Table 4**).

ECI in BC patients is a well-known poor prognostic factor (27,29,34). In our study, although there was no statistically eloquent result between the presence of ECI and survival, the rate of exitus in patients with ECI was 3 times higher than those without (**Table 4**).

According to the study by Kentosborne et al., positive ER and PgR receptors are good prognostic factors for patients. (29,35). Hormone therapy, such as Tamoxifen is applied on the BC patients with positive hormone receptors (27,36). In our study, there was no statistically significant relationship between these receptors and survival, however, in patients with both hormone receptors negative, the mortality was 2 times higher (**Table 4**).

Although the presence of Her2 was considered a poor prognostic factor in patients with BC in the past, these patients are currently treated with trastuzumab (Herceptin) (27,36). BC with negative ER, PgR and Her2 receptors are

known as triple negative and display quite poor prognostic features. Patients who are triple negative frequently present with grade-3 tumors. In our study, we obtained a statistically significant result between Her2 and survival, and the mortality risk of Her 2 positive patients was 8 times higher than those of negative ones (**Table 4**). The presence of LVI is also considered to be a poor prognostic factor (27). In our study, the risk of mortality was found to be approximately 7 times higher in patients with LVI than without (**Table 4**).

In a study of Uncel et al. on BC; due to the heterogeneity of BCs, it has been emphasized that prognostic factors vary according to the molecular subtypes and the individual in these tumors and tailored treatments should be performed (37). In our study, invasive ductal or invasive lobular histopathological types were not statistically significant in relation to survival, but in patients with invasive lobular carcinoma it was found that the risk of mortality was approximately 3 times higher than in patients with invasive ductal carcinoma (**Table 4**).

Owing to the rarity of male BCs, there are few retrospective studies on its etiology, course and treatment. Male BCs exhibit similar clinical features with female BCs encountered in postmenopausal period (38,39). In a retrospective study conducted by Ugurluer et al., all 6 male BC patients undergoing surgery were diagnosed as infiltrative ductal carcinoma histopathologically. Postoperatively, 5 patients received aCT, 3 patients received hormonal therapy and 3 patients received aRT. Metastasis was determined in the follow-up of the patient who did not receive adjuvant therapy (40). Yao et al., compared BC patients receiving and non-receiving adjuvant RT in their study and determined that the group receiving aRT was superior in terms of survival (41). In our study, no recurrence and metastases were found in 3 male BC patients diagnosed with invasive ductal carcinoma and underwent aRT.

In our retrospective study with 120 invasive BC patients, statistically significant findings were obtained between LVI, Her2 positivity, T and N status and OS. In addition, no statistically significant findings could be attained between menopause status, surgical method applied, histopathological type of tumor, presence of ECI, ER and PgR hormone receptors and OS yet their effect on OS was exhibited. Statistically insignificant results are thought to arise from insufficient number of patients incorporated in the study. Early diagnosis with modern imaging methods increases OS in BC, however, the selection of appropriate treatments for suitable patients is crucial.

According to the literature, the prognoses of patients with MRM and BCS are close to each other. However, we could not obtain statistically significant results in our study due to the insufficient number of patients in both groups. In future

studies, it is recommended to keep the number of patients more. Our study is a single center study showing current data.

CONCLUSION

Age, T and N status, applied treatment methods (surgery, CT, RT, hormone therapy, immunotherapy), tumor histopathology and receptor status (ER, PgR, Her2) are considered as prognostic factors in BC. Prognostic factors should be evaluated for each patient before planning treatment in invasive BCs. As a consequence, even though we could not specify enough statistically, we concluded that adjuvant RT positively affected survival in the light of previous studies in the literature and our observations during present study.

Conflict of Interest: In this study, there is no conflict of interest among the authors on any subject.

Ethical Approval: Ethics committee approval taken from the Cukurova University Faculty of Medicine Ethics Committee (Date: 05.04.2019, Session No: 87, Decision No: 68)

Research Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

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