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ORIGINAL ARTICLE

Validity and Reliability Study of James Supportive Care Screening for Cancer Patients

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OBJECTIVE

The present study examined the validity and reliability of the James Supportive Care Screening (SCS), a tool to measure the distress of those diagnosed with cancer, for Turkish patients.

METHODS

After necessary approval was obtained from the oncology hospital, research was conducted with 280 chemotherapy outpatients. Content validity, construct validity, and criterion-related validity tests were used to evaluate validity of SCS use in Turkey, while internal consistency and test-retest reliability were measured to determine reliability.

RESULTS

Content validity index value based on ratings of experts on all items of SCS found on above 0.80. The Turkish version of the scale has 48 items based on 6 factors, and is similar to the original SCS measure. Confirmatory factor analysis . Cronbach's alpha value of scale was 0.918 and unchangeability against time was proven.

CONCLUSION

James Supportive Care Screening is a valid and reliable measurement tool for screening Turkish cancer patients.

Keywords: Cancer; distress; validity; reliability.

Introduction

Cancer is an important chronical disease, mortality rate of which is high, that brings important life changes with it.[1–3] Even though many diagnostic and treatment methods have been recently developed, individuals are confronted with many problems and distress related with them as physically, psychologically, and in social lives.[4–7]

In literature, distress is defined as undesired emotional experiences occurring multidimensional in psyhological (cognitive, behavioral, emotional), social, and spiritual ground that have a negative impact on a patient's coping with the disease.[8] As some researches made to specify the distress experienced my some individuals with diagnosis of cancer are analyzed, it was stated that 51% of 168 individuals diagnosed with cancer were experiencing distress.[9] In a research made by Liao and his friends (2015) over 97 individuals diagnosed with cancer, it was stated that all of the patients experienced distress at intermediate level and that the level of distress had increased dur-

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ing the treatment period.[10] Similarly, in a research made with 500 individuals diagnosed with cancer, it was stated that 50.8% of them experienced distress.[11] As seen in different researches conducted, distress, which is a multidimensional symptom, is seen in individuals diagnosed with cancer at varying rates.[9–13] Furthermore, there are many researches made proving that there are problems that exist causing individuals to experience distress in physical, social, and spiritual areas of life.[14–22]

Thus, the problems experienced by individuals diagnosed with cancer and distress that occur as a result of these problems should be handled together. As each area of life interacts with one another, problems get more complicated while correlation between life quality and disease is being negatively influenced.[23,24] In our country due to reasons like patient density, lack of personal, and not having a standard measurement device for specifying distress in a wide perspective, problems and distress experienced by individuals being diagnosed with cancer can be missed by health professionals while lack of supportive treatment can be seen. One of the most important steps that can be taken to eliminate this deficiency, is to use standard measurement devices specifying distress experienced by the individuals who are diagnosed with cancer in a wide perspective.[6,8,25]

Usage of standard measurement devices will enable for the determination of distress experienced by individuals who are diagnosed with cancer while making it possible for supportive treatment to be provided at an early stage. Supportive care treatment is a special care modeling while family and the individual are taken to the center for all factors, including individual values, beliefs, and cultural issues, to be managed in an effective way.[8] Providing supportive care treatment to the patients, after being diagnosed with cancer, will enable patient's harmonization with the disease and their life quality to be improved.[26,27]

In this research it is aimed for the adjustment of SCS, that measures distress and the problems experienced by individuals in all areas of life in an extensive way, to the Turkish culture and to ensure its validity and reliability. By the usage of a standard measurement device for measuring distress experienced by individuals diagnosed with cancer in our country in clinical environment, it is thought that the problems experienced by individuals won't be missed and that supportive care treatment shall be provided at an early stage.

Materials and Methods

Space and Sampling

For a scale to be considered as a standard measurement tool outside of the country as well, it is required for a validity and reliability study to be conducted including psycholinguistic (language application) and psychometric (validity-reliability) processing.[28,29] Following the approvals received from scale owner, ethical council of the university, and the hospital where the research will be conducted, individuals applying to get chemotherapy treatment at Tülay Aktaş Oncology Hospital as part of Ege University Medical Faculty Hospital, make up the research population. Number of items of SCS are 48. In literature, it is stated that in scale validity and reliability studies, the number of sampling should be at least five times the number of items related with the scale.[30] By taking this information into consideration, the sampling of the research was specified as 280 volunteering individuals composed of outpatients applying to get chemotherapy treatment being over 18 years of ago and not having any physical or mental diseases that could avoid them from understanding or replying questions asked to them. The SCS was read to 280 individuals being diagnosed of cancer, by the researcher himself and the answers given by the individuals have been marked by the researcher. Filling of SCS was completed in 10 minutes on the average.

Data Collection Tools

Introductory Information Form: Introductory information form which is prepared by the researchers by analyzing the literature, is a form composed of 11 questions in total questioning particulars like age, gender, marital status, educational status, occupation, income level, existence of any physical or mental diseases other than cancer, the type of cancer disease, the stage of cancer disease, and the time of being diagnosed with cancer.

James Supportive Care Screening (SCS): The SCS, was developed by Wells-Di Gregorio and his friends (2013) for measuring the distress experienced by individuals being diagnosed with cancer and to specify the areas where they need support. It is composed of 48 items and six subscales in total. Subscales of the scale are composed of emotional concerns (14), spiritual/religious concerns (4), health care concerns (4), social/practical problems (6), cognitive concerns (3), and physical symptoms (17) questions. Scaling questions are answered by using the options of: None (0), mild (1), moderate (2), and severe (3). A total score could be

obtained or evaluations could be made per each question. As the total score increases, the level of distress experienced increases.[31]

EORTC QLQ C-30 Life Quality Scale (European Organisation for Research and Treatment of Cancer Quality of Life): The scale which was developed by European Organisation for Research and Treatment of Cancer, is composed of three sections as functional scale, global health status scale, and symptom scale and it contains 30 questions in total. Total score for scaling could be evaluated or functional scores could be calculated separately as being part of the scaling. The high score which is obtained from functional scales show healthy functional level and high life standard, the high score obtained from global health status scale shows high life quality, and the high score obtained from symptom scale shows that the symptoms are being experienced heavily and that the life quality is low. Turkish validity and reliability of the scale was conducted by Güzelant and his friends (2004) and Cronbach alpha coefficient was found to be ≥0.70.[32,33]

Validity Studies

Linguistic Validity and Content Validity: First of all, original scale has been translated from English to Turkish by five experts (one psychologist, one psychological consultancy specialist, two experts specialized in the nursing related with mental health and diseases, one teacher who is graduated from English Language and Literature Division) by conducting a group translation. The Turkish form which was obtained after the translation was further translated from Turkish to English by two translators, with English being their mother tongue, who have been living in Turkey for many years as a common study conducted by them. The expressions in this translation and the expressions used in original scaling were compared and the required adjustments were done in line with the recommendations made by the translators. In order to ensure content validity, the latest version of scale has been presented to ten experts who knew the technics and methods used in preparing scale questions well. In the evaluation of opinions of experts, Davis technic has been used.[34]

Construct Validity: As relating with the construct validity of the scale, Confirmatory Factor Analysis (CFA), being recommended for scale adjustment works, has been used.[35,36]

Criterion-Related Validity: The correlation between the subscales of SCS, namely emotional concerns, cognitive concerns, and physical symptoms with emotional functional score, cognitive functioning score, and total score of symptom scale of EORTC QLQ C-30 Life Quality Scale has been controlled by calculating pearson moment correlation coefficient.

Reliability Studies

Internal Consistency Analysis: In order to analyze the internal consistency of SCS, Cronbach alpha coefficient of the scale and its subscales and item-total correlation values of the item have been calculated.

Unchangeability against Time (Test-Retest Method): The scale has been reapplied to 30 people after two weeks' time. Analysis was made by calculating the correlation coefficients in the first and final applications.

For the evaluation of data, SPSS and LISREL package programs have been used.

Findings

Findings Relating to Introductory Information

It was determined that among those participating in the research, 65.7% (n=184) were women, 79.6% (n=223) were married, 40.4% (n=113) were junior high school or high school graduates, 44.3% (n=124) were retired, and 50.4% (n=141) had incomes which were in balance with their expenses. The average age of the individuals was specified as 51.92±12.225 years.

It was determined that 38.2% (n=107) of the participants were diagnosed with breast cancer and that among 219 individuals, whose phase was specified (cancer phase of 61 individuals was not determined as it could not be found out yet or due to the missing parts existing in the registry system), 37.1% (n=104) were in the 4th phase and that 31.4% also had physical illness accompanying cancer and that 3.6% (n=10) were also diagnosed with mental illness in addition to cancer. Furthermore, it was determined that the individuals participating in the research were diagnosed with cancer 44.9±4.17 months ago.

Findings Relating with Validity Studies

As the opinions of experts were evaluated by using Davis technic, Content Validity Index (CVI) of all items were found to be over 0.80. In literature, it is stated that as relating with content validity, CVI value of each item should be minimum 0.80.[34] Later on, as regards to face validity, the scale was applied to 15 individuals who were diagnosed with cancer but were not included in the sampling. It was requested from 15 individuals having applied for face validity, to make comments about legibility, understandability, and sorting of scale items.[30] Even though CVI ratio came out to be high-

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Table 1 Standard fit indices of confirmatory factor analysis compare with results of research

Index	Perfect fit criteria	Good fit criteria	Research findings	Result
X^2/SD	0–3	3–5	2.073	Perfect fit index
RMSEA	0.00≤ RMSEA ≤0.05	0.05≤ RMSEA ≤0.10	0.062	Good fit index
CFI	0.95≤ CFI ≤1.00	0.90 ≤CFI ≤0.95	0.91	Good fit index
NNFI	0.95≤ NNFI (TLI) ≤1.00	0.90≤ NNFI (TLI) ≤0.95	0.91	Good fit index
NFI	0.95≤ NFI ≤1.00	0.90≤ NFI ≤0.95	0.90	Good fit index
SRMR	0.00≤ SRMR ≤.05	0.05≤ SRMR ≤0.08	0.07	Good fit index
GFI	0.95≤ GFI ≤1.00	0.90≤ GFI ≤0.95	0.90	Good fit index
AGFI	0.90≤ AGFI ≤1.00	0.85≤ AGFI ≤0.90	0.92	Good fit index

RMSEA: Root mean square error of approximation; CFI: Comparative fit index; NNFI: Non-normed fit index; NFI: Normed fit index; SRMR: Standardised root mean square residual; GFI: Goodness of fit index; AGFI: Adjusted goodness of fit index.

er than 0.80 for all the articles in the scale, in line with the recommendations made by the experts and 15 individuals, minor changes have been made and the scale was given its final form.

Before applying CFA method, in order to determine the sufficiency of sampling, Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) and Bartlett Test of Sphericity tests have been applied and the outcomes were found to be meaningful (KMO= 0.845, X^2=5043.087, p≤0.000). In addition, Power analysis was conducted as Post Hoc and it was seen that the sampling was powerful with a rate of 81.3%.

Following CFA conducted in order to make the evaluation of construct validity, fit indices which are shown in Table 1 and the model relating with Turkish form of the scale illustrated in Figure 1 have been found out. The model which was specified in Turkish, fitted to the original model and it could measure the structure it was aimed to measure with validity in six dimensions as was determined (Table 1 and Figure 1).

A meaningful relationship was found between the subscales of emotional concerns of SCS and the emotional functioning score of EORTC QLQ C-30 Life Quality Scale in the negative correlation and again a meaningful relationship was found between the subscales of cognitive concerns of SCS and the cognitive functional score of EORTC QLQ C-30 Life Quality Scale, in the negative correlation (Table 2). Between the subscales of SCS relating with physical symptoms and the symptom scale of EORTC QLQ C-30 Life Quality Scale, a meaningful relationship was found in the positive correlation (Table 2).

As the total score of SCS was analyzed per gender, it was determined that distress score average was 29.58±19.594 for women and that it was 20.57±16.680 for men.

Findings Relating with Reliability Studies

As Cronbach alpha coefficients of SCS and its subscales were calculated, it was determined that Cronbach alpha coefficient of subscales was above 0.50 and that Cronbach alpha coefficient of the scale was 0.918 (Table 3).

As item-total correlation coefficient of SCS, being composed of 48 items, was analyzed, it was found out that it varied between the values of r=0.665 and r=0.068. Item-total correlation coefficient value of five of the items (13,18,24,28,48) were found to be below 0.20. Among these five items (13,18,24,28,48), only the reliability coefficient of the 28th item was found to be statistically meaningless (p=0.253) (Table 4). As the reliability coefficient of items 13, 18, 24, and 48 was found to be statistically meaningful, regarding these items, no processing was done for removing articles (Table 4). Item 28 was not removed from the scale not to damage the hypothetic structure of the scale[36] and as it could be used in the future studies for analysis.

In order to specify the unchangeability against time (test-retest method) of SCS, the scale was reapplied to 30 individuals two weeks after the first application as regards to parametric statistical testing.[30] As the correlation values obtained after the first and second applications were analyzed, a highly meaningful relationship was found between subscales total scores and total scores of scale, in the positive correlation (Table 5).

Discussion

In order to analyze the construct validity of SCS, in the scale adaptation studies, instead of Exploratory Factor Analysis (EFA), CFA method was used which was seen as a more appropriate method.[36] Before DFA, KMO analysis was done. It was expected for KMO value to

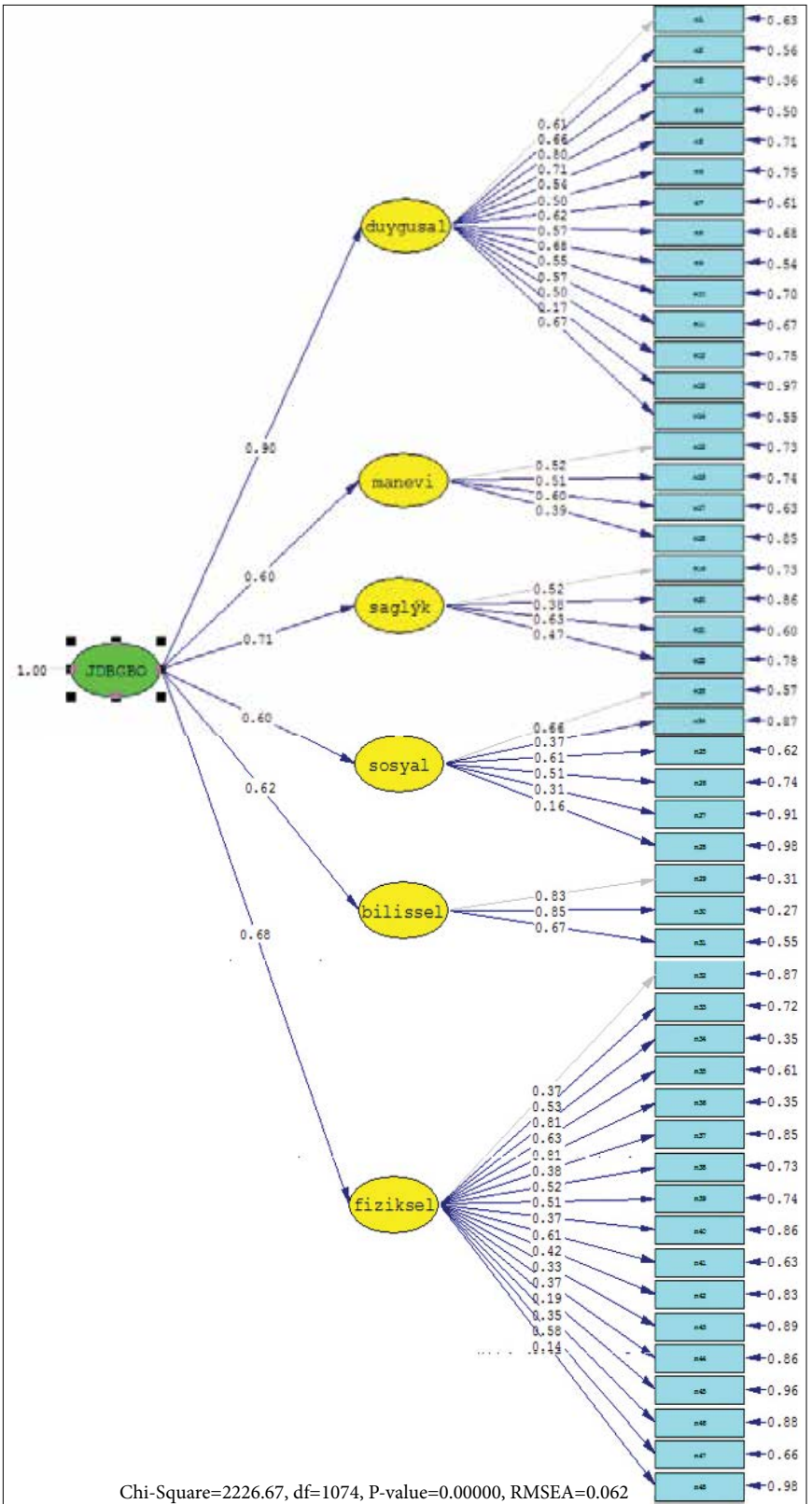

Fig. 1. Defined Model Related 48 items Turkish Form of James Supportive Care Screening.

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Table 2 The relationship between subscales of SCS and subscales of EORTC QLQ C-30 Quality of Life Scale

Correlation value	Emotional concerns subscale of SCS-Emotional Function Score of EORTC QLQ C-30 Quality of Life Scale	Cognitive concerns subscale of SCS-Cognitive Function Score of EORTC QLQ C-30 Quality of Life Scale	Physical symptoms subscale of SCS-Symptom Scale Score of EORTC QLQ C-30 Quality of Life Scale
r	-0.722	-0.751	+0.896
p	0.000**	0.000**	0.000**

**p<0.01.

Table 3 Cronbach alfa coefficients of SCS and subscales

SCS and subscales	Cronbach alfa coefficient
Emotional concerns	0.875
Spiritual/religious concerns	0.549
Health care concerns	0.559
Social/practical problems	0.596
Cognitive concerns	0.826
Physical symptoms	0.837
SCS	0.918

SCS: Supportive Care Screening.

be over 0.60. As values got closer to 1, sampling sufficiency improved. KMO values between 0.80–0,89 are considered as "Good" for sampling sufficiency. KMO value for this research (KMO= 0.845) which was found for this analysis is considered within the range of sampling sufficiency. P value, which was calculated as a result of Bartlett's Test of Sphericity analysis, was found to be ≤0.000. In literature, if p value is below 0.005, it is seen as the correlation matrix's being appropriate for factor analysis. As p value which was calculated as a result of Bartlett's Test of Sphericity analysis was found to be ≤0.000, it was determined that sampling was in accordance with factor analysis. After Power analysis, sampling was found to be powerful with a rate of 81.3%. This outcome met the requirement specified in literature that sampling should be at least powerful with a rate of 80%.[30] As regards to fit indices determined for Turkish modelling following (X^2/df=2.073, RMSEA=0.62, CFI=0.91, NFI=0.90, NNFI=0.91, SRMR=0.07, GFI=0.90, AGFI=0.92), as per literature, X^2/sd was seen as perfect fit index and RMSEA, CFI, NFI, NNFI, GFI, AGFI and SRMR fit indices were seen as good fit indices (Table 1).[37] Furthermore, Turkish modeling illustrated in Figure 1 could measure the structure it was aimed to measure, as valid for the six subscales specified in the original hypothesis (Figure 1).

Between the Emotional concerns subscale of SCS and Emotional functional score of EORTC QLQ C-30 Life Quality Scale, a meaningful relationship in the negative correlation was found (Table 2) and between Cognitive Concerns subscale of SCS and Comprehensive function score of Life Quality Scale of EORTC QLQ C-30, again a meaningful relationship was found in the negative correlation (Table 2). A meaningful relationship was found between Physical symptoms subscale of SCS and Symptom scale score of EORTC QLQ C-30 Life Quality Scale in the positive correlation (Table 2). All of the three correlation values found are above 0.70 (Table 2). If the correlation value is above 0.70, it is interpreted in literature as the validity being high.[30] High score that is obtained from the Emotional functional score of EORTC QLQ C-30 Life Quality Scale shows healthy functional level and high life quality; the high score obtained from Cognitive function score shows high life quality; and the high score obtained from Symptom scale shows that symptoms are experienced heavily and that the life quality is low.[32,33] In SCS, as the score increases, the level of distress also increases.[31] The meaningful relationships found at the research between the subscales of two scales in negative and positive correlation proves the statement in the literature that distress lowers the life quality.[8,12,38]

The numbers of female volunteers participating in the research have been more than the number of male participants. As SCS determines the distress being experienced, it focuses on the emotions.[31] It is thought that the reason why number of volunteer males participating in the research is lower than the number of female volunteers is due to the fact that men tend to express their emotions less than women do.[39–41]

As the total score of SCS is analyzed per gender, it is found out that average distress score of women is higher than that of men. In some researches made in literature, it is also specified that the distress level experienced by women is higher than that of men.[42,43] This finding confirms with the literature.

Table 4 Item-total correlation coefficient value of items in SCS

Items	r	p
Item 1	0.518	0.000**
Item 2	0.496	0.000**
Item 3	0.665	0.000**
Item 4	0.542	0.000**
Item 5	0.539	0.000**
Item 6	0.628	0.000**
Item 7	0.549	0.000**
Item 8	0.492	0.000**
Item 9	0.515	0.000**
Item 10	0.516	0.000**
Item 11	0.399	0.000**
Item 12	0.422	0.000**
Item 13	0.180	0.002*
Item 14	0.580	0.000**
Item 15	0.363	0.000**
Item 16	0.201	0.003*
Item 17	0.290	0.000**
Item 18	0.146	0.014**
Item 19	0.252	0.000**
Item 20	0.225	0.011*
Item 21	0.386	0.000**
Item 22	0.349	0.000**
Item 23	0.442	0.000**
Item 24	0.127	0.034*
Item 25	0.368	0.000**
Item 26	0.294	0.000**
Item 27	0.254	0.000**
Item 28	0.068	0.253
Item 29	0.556	0.000**
Item 30	0.506	0.000**
Item 31	0.446	0.000**
Item 32	0.260	0.000**
Item 33	0.366	0.000**
Item 34	0.651	0.000**
Item 35	0.446	0.000**
Item 36	0.613	0.000**
Item 37	0.304	0.000**
Item 38	0.516	0.000**
Item 39	0.495	0.000**
Item 40	0.369	0.000**
Item 41	0.571	0.000**
Item 42	0.395	0.000**
Item 43	0.352	0.000**
Item 44	0.407	0.000**
Item 45	0.224	0.001**
Item 46	0.307	0.000**
Item 47	0.539	0.000**
Item 48	0.119	0.000**

*p<0.05; **p<0.01.

Table 5 Result of test-retest reliability correlation method of SCS and subscales

SCS and Subscales	r	p
Emotional concerns	0.998	0.000**
Spiritual/religious concerns	0.994	0.000**
Health care concerns	0.984	0.000**
Social/practical problems	0.959	0.000**
Cognitive concerns	0.978	0.000**
Physical symptoms	0.998	0.000**
Total score	0.998	0.000**

**p<0.01.

Cronbach alpha coefficient expected in scale development and adaptation studies in literature is a debatable topic. Cronbach alpha reliability coefficient is only one of the reliability methods. It is not an absolute reliability scale. In some of the researches made in literature, it is stated that Cronbach alpha value should not be lower than 0.50.[44,45] Cronbach alpha values of all subscales of SCS were found to be above 0.50. Furthermore, in some of the studies Cronbach alpha values in between 0.40 and 0.60 are seen to reflect low reliability.[30,46] Cronbach alpha coefficients of subscales of Spiritual/Religious concerns, Health care concerns, Social/practical problems of SCS were determined to be within low reliability interval (Table 3).[30] Numbers of articles in these three subscales vary between 4 and 6. As the number of articles decrease, Cronbach alpha coefficient falls down. It is though that this is the reason why Cronbach alpha value of subscales with less number of articles is lower than that of subscales with higher number of articles. [46] Total Cronbach alpha value of SCS was found to be within the high reliability interval of 0.80–1.00 and it was specified as 0.918 (Table 3).[30]

The item-total correlation coefficient value of five items (13,18,24,28,48) of SCS was determined to be below 0.20. In literature, it is stated that item-total correlation value should be higher than 0.20.[30] Except for that of article 28 in this five items, the item-total correlation reliability coefficient of all of the items were found to be statistically meaningful (Table 4). As the reliability coefficient of articles with item-total correlation value lower than 0.20, the item-total correlation reliability coefficient was found to be statistically meaningful in the research conducted by Bilge (2006) as in this research, no processing was not to eliminate any articles.[47] Only the item-total correlation reliability coefficient (p=0.253) of article 28 which was calculated

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after item-total correlation was found to be statistically meaningless (Table 4). In literature it is specified that omission of an article damages the hypothetic structure of the original scale while adjusting a scale which was developed priory.[36,48] For this reason, no omission was made for article 28. The total item correlation value of this article will be reviewed again in the future studies to be conducted. In case similar results are obtained, omission of article could be made together with the scale owner by conducting a intercultural study and by repeating validity and reliability studies.[36,48]

As the relationship between measurements of SCS for the beginning study and for the one applied two weeks later was analyzed, the correlation value specifying the relation between all subscales and scale total score was found to be in the perfect reliability interval of 0.95 and 1.00 (Table 5).[30] With the correlation values found, the unchangeability of scale against time was proven.

Conclusion

The SCS is composed of six subscales and 48 questions in the total. After the adjusted study was conducted, it was proven that the scale is a valid and reliable measurement tool for this sampling group of Turkish community. It is recommended for the scale to be implemented for wider sampling groups in the future studies and for the item-total correlation correlation value of item 28 to be reviewed again. Additionally, on the original form of the scale, there are 8 pieces of clinical questions which were not included in the scale scoring. In the studies where the scale will be applied, these questions and the clinical questions could also be used to avoid any problems to be missed.

Disclosure Statement

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Impact of Peritumoral Edema on Overall Survival in Glioblastoma Multiforme

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OBJECTIVE

The aim of the present study was to investigate the relationship between peritumoral edema and overall survival in glioblastoma multiforme (GBM).

METHODS

Total of 101 patients with radiologically or pathologically GBM were included in this study. Data of patient age, sex, tumor dimensions, and preoperative peritumoral edema were analyzed.

RESULTS

While average survival was 16.67±3.99 months (95% confidence interval [CI]: 8.85-24.49 months) and 1- and 3-year survival rates were 50% and 16.7%, respectively, for patients without edema, average survival was 13.74±1.95 months (95% CI: 9.91-17.58 months) and 1- and 3-year survival rates were 35.6% and 8.5%, respectively, for patients with edema. No statistical difference between them was found (p=0.297).

CONCLUSION

Prognostic value of edema for survival could not be determined in this retrospective analysis of homogeneous group of patients with isolated GBM.

Keywords: Glioblastoma multiforme; peritumoral edema; survival.

Introduction

Although brain tumors are a significant morbidity and mortality reason relatively common in adults, metastatic tumors are seen most frequent in brain.[1] More than half of brain tumors are malign glioms (WHO Grade III-IV) and approximately 3/4 of them are grade IV glioblastoma multiforme (GBM).[2] While it can be seen at every age, it peaks between 45 and 55 years of ages.

GBM's standart treatment is surgical. The main aim of surgical treatment is a complete surgical excision which has a direct relationship with disease-free survival and overall survival.[3,4] However, because GBM has a high local recurrence rate, there is a need for adjuvant therapies after surgical treatment. In the Stupp and his colleagues' joint randomized phase III study with European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) groups, it is shown that adding temozolomide (TMZ) (75 mg/m^2) which is an oral alkylating agent and 5 cures (150–200 mg/m^2) of adjuvant therapy simultaneously to the standart conventional radiotherapy (RT) extends the survival significantly compared

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to the RT alone. Nowadays, GBM patients' standart treatment is determined like "complete surgical excision+simultaneous chemoradiotherapy+adjuvant chemotherapy".[5,6]

In high grade tumors age, KPS, histology, resection width, duration of symtomes, neurological-functional mental state and tumor's crossover to the opposite lobe are defined prognostic factors.[7–11] Our intention in this study is to observe peritumoral edemas' effect to the survival in GBM.

Materials and Methods

101 patients that medical inoperable ones' GBM diagnosis were made by radiologically, operated ones' GBM diagnosis were made by pathologically and RT and simultaneously chemotherapy (CT) were applied and monitored for adjuvant therapy, are included in this study. The patients age, sex, tumor's dimensions and peritumoral edema were recorded.

Treatment

Computer tomography scans were done for RT applicaton. The mass or mass loge was fusioned with MRG which has had before surgical treatment. Brainstem, lenses, optical nerrves, pituitary gland and optical chiasm were contoured as critical organs.

The 3 dimensional conformal radiotherapy (3DRT) or intensity modulated radiotherapy (IMRT) techniques were used. In RT planning, if there wasn't an edema, the mass or mass bed was described as the GTV2 in terms of gross tumor volume (GTV), if there was an edema, it is described as the GTV1 including that. The clinical tumor volume (CTV) was forged with 2 cm margins given to the GTV1 or GTV2. The CTV was excluded from anatomic barriers if there was not an extension. The planned target volume (PTV) was forged with 0.5 cm margins given to the CTV. 2 Gy each for 23 fractions total 46 Gy were given to the PTV1, 2Gy/7 fractions total 14 Gy were given to the PTV2 and grand total tumor dose reached to 60 Gy. Everyday orally 75mg/m^2 TMZ was applied as simultaneously CT. After RT, once in 28 days, 5 days long 150–200mg/m^2 TMZ was applied for 5 cures.

Follow-up

After RT, clinical examination, complete blood test and MRG controls were done with 2 months periods. The overall survival was accepted as the time between diagnosis and last control or death date.

Statistical methods

The obtained data was loaded to the SPSS 13.0 softwere. The Kaplan-Meier test was used for survival times. The prognostic factors were calculated with the long-rank test. P<0.05 was accepted as significant.

Results

39% (39) of 101 patients that involved to the study were females and 61% (62) of them were males. The age average was 62.72±13.56 (7–88). 15 (15%) patients were <50 years old, 86 (85%) of them ≥50 years old.

The average tumor size was 4.03±1.46 cm (1.5–8.0) and at 59 (58%) patients ≤4 cm and at 42 (42%) of them >4 cm. Because they were medical inoperable at 23 (23%) patients diagnosis was made by radiologically. 23 (23%) of the 78 (77%) patients who were operated, only biopsy was applied. Subtotal excision was made to 21 (21%) patients and total excision was made to 34 (33%) of them. The drawn volumes at the RT planning; the mass was 92.03±107.58 (13.65–721.21) cm^3, PTV 0–46 544.88±240.19 (50.91–1257.85) cm^3 and PTV 46–60 319.45±172.32 (19.81–899.96) cm^3. If it was evaluated based on sex; while the average survival at females was 13.45±2.13 (95% CI: 9.28–17.63) months, and 1 and 3 years survival rates were 33.6% and 5.7% respectively, the average survival at males was 13.95±2.06 (95% CI: 9.91–17.98) months and 1 and 3 years survival rates were 37.7% and 9%, and there were no statistically difference between them. If the survival was evaluated based on age; while the average survival was 24.83±3.01 (95% CI: 18.91–30.75) months, 1 and 3 years survival rates were 79% and 15% respectively at the patients below 50 years old, the average survival was 11.44±1.56 (95% CI: 8.38–14.50) months, 1 and 3 years survival rates were 28.7% and 5.6% respectively and, there was a statistically significant difference between them (p=0.001). If the survival was evaluated by tumor size; while at the patients ≤4 cm the average survival was 8.13±2.24 (95% CI: 3.72–12.53) months, 1 and 3 years survival rates were 35.9% and 14% respectively, at the patients >4 cm survival was 11.49±1.62 (95% CI: 8.32–14.67) months, 1 and 3 years survival rates were 39.5% and 0%. A significant relation between tumor size and survival couldn't be found (p=0.0404). While the average survival at the patients who were treated without surgical operation was 9.50±2.05 (95% CI: 5.46–13.53) months, 1 and 3 years survival rates 24.8% and 0% respectively, the average survival at the patients who were applied biopsy and subtotal excision was 11.88±1.62 (95% CI: 8.38–14.50) months, 1 and 3

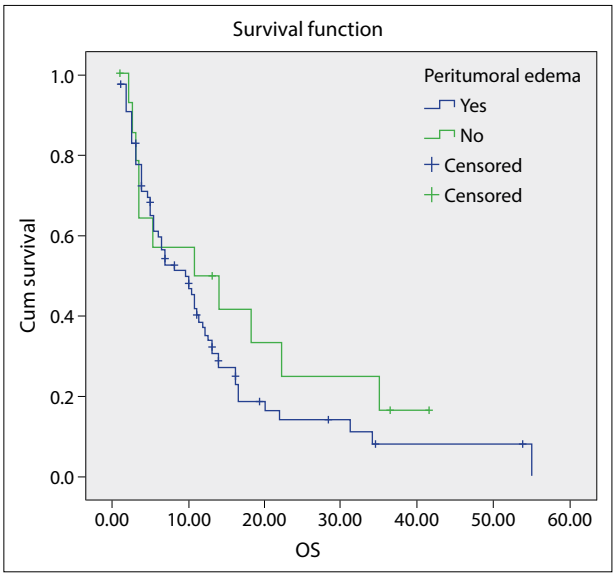

Fig. 1. Overall survival.

years survival rates were 39.1% and 3.3% respectively, the average survival at the patients who were applied total excision was 19.62±3.82 (95% CI: 12.13–27.12) months, 1 and 3 years survival rates were 39.3% and 23.9% respectively and, a statistically significant relation between them couldn't be found (p=0.099).

While there was no peritumoral edema at 15 (15%) patients, at 86 (85%) of them there was an edema and the average volume of the edema was 145.71±133.92 (0.0–549.80) cm^3. If the survival was evaluated for peritumoral edema at the GBM patients; while the average survival was 16.67±3.99 (95% CI: 8.85–24.49) months, 1 and 3 years survival rates were 50% and 16.7% respectively at the patients without edema, the average survival was 13.74±1.95 (95% CI: 9.91–17.58) months, 1 and 3 years survival rates were 35.6% and 8.5% respectively at the patients with edema and, there wasn't a statistical difference between them (p=0.297) (Figure 1).

If the peritumoral edema was evaluated for sex; while there was no peritumoral edema at 5 female patients, at 34 of them there was an edema. The edema seen rate at females was 87%. The average survival of female patients without edema was 21.40±7.32 (95% CI: 7.04–35.75) months, 1 and 3 years survival rates were 50% and 25%, the average survival of female patients with edema was 11.44±1.91 (95% CI: 7.69–15.20) months, 1 and 3 years survival rates were 33.8% and 0% respectively. There was no statistical difference between two groups (p=0.145). While the edema wasn't observed at 10 male patients, at 52 of them it was observed. The edema rate at male patients was 83%. The average survival of male patients without edema was 13.79±4.18 (95% CI: 5.58–22.0) months, 1 and 3 years survival rates were 50% and 12.5%, the average survival of male patients with edema was 14.42±2.64 (95% CI: 9.23–19.61) months, 1 and 3 years survival rates were 34% and 10.4% respectively. There was no statistical difference between two groups (p=0.406). If all groups compared with each other, there was no statistical difference between them (p=0.619).

If the peritumoral edema was evaluated for age; while there was no peritumoral edema at 4 patients under ages of 50, at 11 of them there was an edema and, edema seen rate was 73%. The average survival was 26.99±4.63 (95% CI: 17.91–36.07) months, 1 and 3 years survival rates were 75% and 25% respectively at the patients under 50 years with no edema. The average survival rate was 23.91±4.10 (95% CI: 15.87–31.96) months, 1 and 3 years survival rates were 70.7% and 0% respectively at the patients under 50 years with edema. There was no statistical difference between two groups (p=0.800). The average survival rate was 12.15±4.49 (95% CI: 3.33–20.96) months, 1 and 3 years survival rates were 30% and 15% respectively at the patients 50 years old and over with no edema. The average survival rate was 11.04±1.53 (95% CI: 8.02–14.06) months, 1 and 3 years survival rates were 30.1% and 4.3% respectively at the patients 50 years old and over with edema. There was no statistical difference between two groups (p=0.918). But, if all groups were compared, there was a statistical difference (p=0.034).

If the peritumoral edema was evaluated for tumor size; while there was no edema at 6 patients with a tumor ≤4 cm, at 53 of them there was an edema. The edema seen rate was 90%. The average survival was 19.98±8.0 (95% CI: 4.30–35.66) months, 1 and 3 years survival rates were 40% and 40% respectively at patients with a ≤4 cm tumor without an edema. The average survival was 14.77±2.42 (95% CI: 10.02–19.51) months, 1 and 3 years survival rates were 35.5% and 10.2% respectively at patients with a ≤4 cm tumor and an edema. There was no statistical difference between two groups (p=0.426). While there was no edema at 9 patients with a tumor >4 cm, at 33 of them there was an edema. The edema seen rate was 79%. The average survival was 14.12±4.05 (95% CI: 6.16–22.08) months, 1 and 3 years survival rates were 55.6% and 0% respectively at patients with a >4 cm tumor without an edema. The average survival was 8.71±1.04 (95% CI: 6.65–10.76) months, 1 and 3 years survival rates were 34.3% and 0% respectively at patients with a >4 cm tumor and an edema. There was no statistical difference

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between two groups (p=0.141). If all groups compared with each other, there couldn't be found a statistical difference (p=0.259).

If it was evaluated for surgical operation; because 23 (23%) of the patients were accepted as medical inoperable, the diagnosises were made radiologically. While at 6 of these patients there was no edema, at 17 of them there was an edema. The edema seen rate was 74%. The average survival was 12.10±4.91 (95% CI: 2.47–21.73) months, 1 and 3 years survival rates were 33.3% and 0% respectively at the group with no edema. The average survival was 8.55±2.21 (95% CI: 4.21–12.89) months, 1 and 3 years survival rates were 26.8% and 0% respectively at the group with an edema. There was no statistical difference between two groups (p=0.571). While at 6 of the patients who were applied biopsy and subtotal excision there was no edema, at 38 of them there was an edema. The edema seen rate was 86%. The average survival was 12.60±5.98 (95% CI: 0.86–24.34) months, 1 and 3 years survival rates were 40% and 20% respectively at the group with no edema. The average survival was 11.61±1.62 (95% CI: 8.42–14.80) months, 1 and 3 years survival rates were 34.5% and 0% respectively at the group with an edema. There was no statistical difference between two groups (p=0.588). While at 4 of the patients who were applied total excision there was no edema, at 30 of them there was an edema. The edema seen rate was 88%. The average survival was 31.93±6.83 (95% CI: 18.53–45.33) months, 1 and 3 years survival rates were 100% and 50% respectively at the group with no edema. The average survival was 18.18±3.88 (95% CI: 10.57–25.80) months, 1 and 3 years survival rates were 39.4% and 24.3% respectively at the group with an edema. There was no statistical difference between two groups (p=0.141). If all groups compared with each other, there couldn't be found a statistical difference (p=0.167). Table 1 demonstrates patient characteristics and results of log-rank univariate analysis for overall survival.

Discussion

The GBM is most common primary malign brain tumor. The first priority treatment at this disease is the maximal safe resection. The relationship between surgical resection's width and survival was shown in previous surgical series. Because the local recurrences inevitable, it is breeding a need for an adjuvant treatment. The first RT studies related with the adjuvant treatment is the wide area (whole brain) irradiations in the literature. It is shown the RT's positive affect to the survival at the comparison of the patients who have whole brain RT after surgical treatment and the patients who didn't have any adjuvant therapy. But, because of the brain's tolerance dosage, lower dosages were used at these wide area irradiations. Later, at the otopsy series, by reason of the disease's recurrences' 90% were being at the first 2 cm and were being shown the tumor cells' existance in the peritumoral edema tissue, it was started to apply higher dosages to more limited areas and it was determined that there was an advantage on survival with these applications.[12] However it was tried many agents for a systemic treatment, the breaking point at this field which is determining nowadays' standarts was held by Stupp and his colleagues[5] in 2005 by the application of 75 mg/m^2 TMZ simultaneously with 60 Gy RT. The most evident response was seen at the patients who had MGMT mutation. Today, even though many tests were made with new technologies and new devices like dosage escalation and/or additional dosage stereotactic boost, there is no randomized evidence that shows efficacy of over 60 Gy dosages yet.

It was come to a certain point at systemic treatment as well as local treatment on GBM and it couldn't be gone beyond Stupp's study.[6] It is similar for prognostic factors. The RPA classification is still remains the feature of being the most used and the most valid classification. The age, performance state, resection width, duration of symptoms, neurologic-functional mental state and tumor's cross over status to the other lobe are the best known prognostic factors. The publications about the peritumoral edema's being a prognostic factor question that's our study's main goal as well, are controversial. Although it is already known that there are tumoral cells surrounding the tumor's edema and included to the RT literature, being inevitable of the local recurrences directed us to search this subject.

The necrosis MR is one of the pathognomonic factors for GBM, too. Also, the peritumoral edema's being wide situation at these tumors is a frequent situation at diagnosis phase or at the patients not having stereoids. It is being thought that the widespread edema at the diagnosis phase is related with the tumor's biological behaviour. Wu and his colleagues reported that at the retrospective analysis which they examined 109 patients' with malign glioma preoperative MR images, the edema and necrosis were negative prognostic indicators for overall survival. Also, they suggested these tumor cells in the peritumoral edema area could be related to the unresponsiveness to the treatment. It was indicated that this peritumoral edema's effect was controversial in the Liu and his colleagues' study.[13] Even it was stated

Table 1 Patient characteristics and results of log-rank univariate analysis for overall survival.

	Peritumoral edema	n	Overall survival	1 year survival (%)	3 years survival (%)	p	
General	No	15	16.67±3.99 (95% CI: 8.85–24.49)	50	16.7		0.297
	Yes	86	13.74±1.95 (95% CI: 9.91–17.58)	35.6	8.5		
Sex							
Female	No	5	21.40±7.32 (95% CI: 7.04–35.75)	50	25	0.145	
	Yes	34	11.44±1.91 (95% CI: 7.69–15.20)	33.8	–		0.619
Male	No	10	13.79±4.18 (95% CI: 5.58–22.0)	50	12.5	0.706	
	Yes	52	14.42±2.64 (95% CI: 9.23–19.61)	34	10.4		
Age							
<50	No	4	26.99±4.63 (95% CI: 17.91–36.07)	75	25	0.800	
	Yes	11	23.91±4.10 (95% CI: 15.87–31.96)	70.7	–		0.034
≥50	No	11	12.15±4.49 (95% CI: 3.33–20.96)	30	15	0.916	
	Yes	75	11.04±1.53 (95% CI: 8.02–14.06)	30.1	4.3		
Tumor size							
≤4 cm	No	6	19.98±8.00 (95% CI: 4.30–35.66)	40	40	0.426	
	Yes	53	14.77±2.42 (95% CI: 10.02–19.51)	35.5	10.2		0.259
>4 cm	No	9	14.12±4.05 (95% CI: 6.16–22.08)	55.6	–	0.141	
	Yes	33	8.71±1.04 (95% CI: 6.65–10.76)	34.3	–		
Treatment							
Radiological	No	6	12.10±4.91 (95% CI: 2.47–21.73)	33.3	–	0.571	
	Yes	17	8.55±2.21 (95% CI: 4.21–12.89)	26.8	–		
Biopsy-subtotal	No	6	12.60±5.98 (95% CI: 0.86–24.34)	40	20	0.588	0.167
	Yes	38	11.61±1.62 (95% CI: 8.42–14.80)	34.5	–		
Total	No	4	31.93±6.83 (95% CI: 18.53–45.33)	100	50	0.141	
	Yes	30	18.18±3.88 (95% CI: 10.57–25.80)	39.4	24.3		

that the radiological differences of the malign gliomas including histological differences could be causing this debate. The sharpness of the boundaries of the edema surrounding the mass was also examined but it lost the meaningfulness in the multivariant analysis.

Wu CX and his colleagues[14] study, the enhancement extent was associated with the OS of the patients with malignant glioma on univariate analysis, while it failed to retain its significance on multivariate analysis. Schoenegger K et al.[15] results confirm that peritu-

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moral edema on preoperative MRI is an independent prognostic factor in addition to postoperative Karnofsky performance score (KPS), age, and type of tumor resection. Patients with major edema had significant shorter overall survival compared to patients with minor edema.

The results of our study are inconclusive; the available evidence does not certainly support or rule out an association between pre-operative peritumoral edema and overall survival (p=0.297). However, the patients under 50 years with no edema had significant long overall survival compared to patients 50 years old and over with edema (p=0.034).

For a conclusion, the edema's prognostic value couldn't be determined on the survival in the retrospective analysis of our homogeneous group formed from isolated GBM patients. There is a need for randomized studies with higher patient numbers for researching this subject.

Disclosure Statement

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Evaluation of Pulmonary Function After Radiotherapy Using Helical Tomotherapy for Breast Cancer Treatment: Prospective Study

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OBJECTIVE
Purpose of the present study was to investigate acute pulmonary changes using pulmonary function tests (PFTs) after breast cancer irradiation with helical tomotherapy (HT).

METHODS
Forty patients were included in this study. Pretreatment and 3 months after completion of radiotherapy (RT), values of forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and FEV1/FVC ratio were measured and recorded.

RESULTS
Restrictive pattern was seen in 4 patients in baseline PFTs and moderate deterioration was observed in their measurements of PFT at 3 months after RT. Obstructive pattern was defined in only 1 patient in baseline PFTs and it remained unchanged after RT. Mild obstructive pattern in 4 patients and mild restrictive pattern in 3 patients had developed at 3 months after RT.

CONCLUSION
Minimal changes that result in mild restrictive and obstructive pattern in PFTs can be seen in acute phase after RT with HT.

Keywords: Breast cancer; radiation pneumonitis; tomotherapy.

Introduction

Radiation-induced lung disease (RILD) is one of the most common clinical toxicities resulting from thoracic radiotherapy. The cells in the alveolar space are damaged by radiation and early damage progresses to an acute exudative inflammation process. In this way, radiation pneumonitis (RP) is manifested within 4–12 weeks after completion of radiotherapy.[1] Subclinical acute lung injury is experienced by most of these patients. Pulmonary function test (PFT) is a useful tool to assess the respiratory impairment and pulmonary function is com-

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monly measured by evaluating the FVC, FEV1, FEV1/FVC.[2] The main factors responsible for pulmonary toxicity are irradiated lung volume and radiation dose. Although the strong correlations between the different dosimetric parameters, there is no sharp threshold dose (Vdose) associated with RP risk due to different radiation techniques and applications.[3] Conventional 3D conformal radiotherapy (3DCRT) that use parallel-opposed tangential beams is most common technique in breast cancer irradiation and it's complications are well documented. In breast cancer irradiation, the increased use of recent more sophisticated radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) and helical tomotherapy (HT) allows complex treatment plan according to patient's anatomy. Particularly HT use all gantry angles because of rotational delivery and it could cause low doses to a greater volume of healthy tissues, especially the contralateral breast and lung. The current question is how these techniques will impact clinical outcomes. These techniques have been evaluated and demonstrated dosimetric advantages in many studies.[4–6] However, to our knowledge, presence of acute lung injury in breast cancer irradiation using HT has been investigated prospectively in very few studies,[7] although many studies[8–14] including different RT techniques have shown changes in pulmonary functions after breast and mostly lung cancer irradiation. The purpose of this prospective study was to investigate acute pulmonary changes that could be caused radiotherapy using pulmonary function tests (PFTs) in breast cancer patients treated with HT.

Materials and Methods

Patients

Between April 2015 and September 2015, proven histopathologic features of breast cancer, age 18–75 years and stage I–III, female patients who were performed breast conserving surgery or mastectomy and required adjuvant radiotherapy were intended to include in this prospective study after obtaining informed consent. The exclusion criteria were a history of chronic respiratory disease, previous RT to thorax, concomitant malignancy, the presence of respiratory symptoms for more 2 weeks within previous one year. Ultimately, 56 patients met the selection criteria for this study that was approved by local research ethic board. Forty patients completed both PFTs at two time points. All patients underwent complete blood count, chest radiograph and PFTs pre-RT and 3 months after completion of RT to evaluate baseline status and acute pulmonary changes.

Radiotherapy

All patients were positioned using a breast board (CIVCO) with their head turned to the contralateral side and the ipsilateral arm raised above their head in a supine position and computed tomography (CT) images with 3.0 mm thickness were obtained for RT planning. For whole breast or chest wall RT with or without lymph nodes, the planning target volume (PTV) and critical structures including the ipsilateral and contralateral lung, heart, esophagus, spinal cord, contralateral breast and skin were defined and contoured according to the recommendations of the breast cancer atlas for radiation therapy planning consensus definitions of RTOG (the Radiation Therapy Oncology Group) (available at: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx). The lumpectomy bed was also contoured as a boost PTV with 1cm expansion in the patients were performed breast-conserving surgery and 10 or 16 Gy was prescribed as boost dose for 13 lumpectomy cavity and 4 incision scar. In the case of lymph node positivity, lymphatic PTV was created. Loco-regional RT volume was defined as the axillary and supraclavicular lymph nodes with or without ipsilateral internal mammary nodes additional to the chest wall or breast. Local RT was defined as target volume of the chest wall or breast. The volume contours and CT images were transferred to the Tomotherapy H system (Accuray Inc., Sunnyvale, CA) to create treatment plans. TH plans were created with a field width of 5.048 cm, fixed jaw mode and a pitch of 0.287. The median modulation factor was 3.0 and it ranged from 2.0 to 3.5. Dose prescription was 50 Gy in 25 fractions of 2.0 Gy daily.

Evaluation of Radiation Doses

As dose constraints for the PTV, 1) D95 was defined as the minimum dose delivered to 95% of the PTV and D95 ≥95% of the prescribed dose were satisfied. 2) V95% (V47.5 Gy) was defined as the percentage of the PTV receiving at least 95% of the prescribed dose and V95% ≥ 95% were satisfied. For PTV, the parameter V107 (V53.5 Gy) was defined as the percentage of the PTV receiving at least 107% of the prescribed dose and was used to assess the maximum doses. Dose-volume histograms (DVHs) for the PTV, lung and the heart were calculated for each patient. Ipsilateral and total mean lung dose (MLD), ipsilateral lung volume receiving 5 and 20 Gy (V5 and V20), values of mean dose, V5, and V30 of the heart derived from DVHs were evaluated.

The Conformity Index (CI) was calculated as the ratio of the V95% over the volume of breast or chest

Table 1 Baseline patient and treatment characteristics

Variable		n	%
Age			
Mean±SD	47.47±10.12		
Range	25–71		
<50 y		22	55.0
≥50 y		18	45.0
Smoking history			
Smokers		10	25.0
Non smokers		30	75.0
Histology			
Invasive ductal carcinoma		32	80.0
Invasive lobular carcinoma		3	7.5
Tubulo-lobular carcinoma		2	5.0
Others		3	7.5
Stage			
IA		3	7.5
IIA		9	22.5
IIB		10	25.0
IIIA		12	30.0
IIIB		4	10.0
IIIC		2	5.0
Tumor side			
Right breast cancer		22	55.0
Left breast cancer		18	45.0
Surgery			
Partial mastectomy		15	37.5
Modified radical mastectomy		25	62.5
Chemotherapy			
Adjuvant		34	85.0
Neo-Adjuvant		3	7.5
Both		2	5.0
No chemotherapy		1	2.5
Chemoterapy regime			
AC+Taxan		19	47.5
Taxan		11	27.5
FEC+Taxan		7	17.5
AC		1	2.5
FEC		1	2.5
No chemotherapy		1	2.5
Hormone therapy			
Aromatase inhibitor		11	27.5
Tamoxifen		20	50.0
No hormone (Receptor negative)		9	22.5
Concurrent trastuzumab			
Yes		17	42.5
No		23	57.5

AC: Adriamycin, cyclophosphamide; FEC: 5-Fluorouracil, epirubicin, cyclophosphamide.

wall PTV. The Homogeneity Index (HI) was calculated by the following formula.

HI=(D2%–D98%)/D50%

Chemotherapy and Hormone therapy

Thirty nine patients had been given neoadjuvant and/or adjuvant chemotherapy including anthracycline and/or taxan-containing regimens. The patients had hormone receptor positivity were given aromatase inhibitor or tamoxifen with or without luteinizing hormone-releasing hormone (LHRH) analogue after completion of RT. One patient with partial mastectomy received tamoxifen plus LHRH analogue but not chemotherapy because she had stage IA disease. The patients whose were Her2 (3+) and Silver Enhanced In Situ Hybridization (+) (SISH+) in the case of Her2 (2+) received concomitant Trastuzumab with RT and were continued 1 year after completion of RT.

Pulmonary Function Tests

Evaluation of pulmonary function was based on spirometric measurement (ZAN 300: ZAN Messgerate GmbH, Oberthulba, Germany). Pre-treatment and 3 months after completion of RT, values of forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and FEV1/FVC ratio were monitored and recorded as percentages of predicted values. All tests were assessed the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS).[15]

Statistical analysis

Data were analyzed using SPSS version 16.0 statistical software (SPSS, Chicago, IL, USA). All data were expressed as median and/or mean±standard deviation. Patients' demographic, clinical and dosimetric data were analyzed using Kolmogorov-Smirnov to test whether for normal distribution. Since variables were non-normally distributed and/or were ordinal, correlation coefficients and their significance were calculated using Spearman test to examine the strength of the relationship between variables at two time points. The Wilcoxon test was used to test the significance of dependent variables between pre-treatment and 3 months after RT. Mann–Whitney U test was used to identify the relation between independent groups such as age (<50 and ≥50 years), RT volume (local RT and loco-regional RT), ipsilateral lung volume receiving dose ≥20 Gy (V20, ≥20% and <20%, ≥25 and <25, ≥30 and 30), use of tamoxifen (yes and no) and also use of concomitant Trastuzumab (yes and no).

Results

Baseline patient and treatment characteristics were summarized in Table 1. Dosimetric parameters of

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Table 2 Dosimetric parameters of PTV and organs at risk

Parameter	Mean±SD	Median	Range
Treatment time (min)	6.82±3.03	6.10	3.8–17.9
PTV			
Dmean	52.19±1.48	51.67	50.30–56.37
Dmin	35.95±4.79	36.58	18.14–42.49
Dmax	59.10±4.44	56.86	54.37–70–18
V95	97.44±2.14	97.45	87.63–100.00
V107	26.34±25.11	19.17	0.42–75.96
CI	0.97±0.25	0.97	0.88–1.05
HI	0.20±0.09	0.18	0.07–0.38
Ipsilateral lung			
Dmean	14.94±2.57	15.22	6.93–20.52
V5	83.16±16.64	84.94	22.45–100.00
V20	24.30±5.55	25.35	10.41–34.68
Contralateral lung			
Dmean	7.00±2.25	7.09	1.24–11.25
V5	56.53±22.44	56.03	0.00–100.00
V20	2.23±3.15	1.12	0.00–13.23
Total lung			
Dmean	11.29±2.07	11.54	4.36–16.22
Heart			
Dmean	9.32±2.14	9.25	0.50–13.42
V5	77.87±24.70	83.71	0.00–100.00
V25	2.94±2.74	2.61	0.00–9.74
V30	1.52±1.75	0.65	0.00–6.50
Contralateral breast			
Dmean	6.30±1.84	6.51	0.46–9.81

SD: Standart deviation; Vx: Volume (%) receiving x dose (Gy) or higher; Dmax: Maximum dose; Dmin: Minimum dose; Dmean: Mean dose; CI: Conformity index; HI: Homogeneity index.

PTV and organs at risk were presented in Table 2. The target dose homogeneity and conformity index were perfect in this study. PFTs measurements pre-RT and 3 months after RT and comparison of parameters between two time points were presented in Table 3. Means of percent of decrease in FEV1 and FVC was found as 0.06±0.07 and 0.06±0.06, respectively. There were statistically significant changes in PFTs at 3 months after RT ($p<0.05$). We compared the means of percent decrease in FEV 1 and FVC from before RT to 3 months after RT in subgroups (Table 4). In the patients were given concurrent Trastuzumab with RT and the group had the value of ipsilateral lung V20 was ≥30, mean of percent decrease in FVC at 3 months after RT was significantly higher ($p= 0.022$ and $p=0.019$, respectively). However, age, RT volume and use of tamoxifen had no effect on means of percent decrease in FEV 1 and FVC from before RT to 3 months after RT. In correlation analysis, there was no statistically significant correlation between irradiated lung volumes including values of total lung Dmean, ipsilateral lung Dmean, V5 and V20 and measurements of PFT at 3 months after RT ($p>0.05$). However, there was negative correlation between age and FEV1/FVC at 3 months after RT ($r=-0.321$ and $p=0.043$). The patients were diagnosed with neither clinical nor radiological pulmonary complications after RT during the study period. According to baseline measurements of PFT, restrictive pattern was seen in 4 patients and a moderate deterioration was observed in their measurements of PFT at 3 months after RT. In the evaluation at 3 months after RT, mild restrictive pattern newly developed in 3 patients additional to 4 patients at baseline. The obstructive pattern was defined in only one patient in baseline PFTs and it remained unchanged after RT. Additional to this patient, mild obstructive pattern was developed in 4 patients at 3 months after RT. Table 5 shows characteristics of these restrictive and obstructive patients.

Table 3 Parameters of pulmonary function tests and hemogram at two time points and results of Wilcoxon Test

PFT	Pre-RT (T0)		At 3 mo after RT (T1)		Comparison of T0 and T1
	Median	Range	Median	Range	p
FVC (%)	93.00	58–117	88.00	49–120	0.000
FEV1 (%)	89.00	52–122	82.50	49–120	0.000
FEV1/FVC (%)	84.0	65–108	84.00	64–106	0.073
Hemoglobin	11.87	7.32–13.40	12.58	10.06–14.28	0.000
WBC	6.90	2.93–40.95	6.01	3.10–9.93	0.002
Platelet	288.35	164.00–478.20	231.15	140.90–307.70	0.000

PFT: Pulmonary function test; FVC: Values of forced vital capacity; FEV1: Forced expiratory volume in first second; WBC: White Blood Cell; RT: Radiotherapy.

Table 4 Comparison of mean of percent decrease in FEV 1 and FVC from before RT to 3 months after RT by using Mann Whitney U Test in subgroups

Group	n	Change in FEV1 p	Change in FVC p
Age		0.22	0.24
<50 y	22		
≥50 y	18		
Concurrent trastuzumab		0.05	0.02
YES	17		
NO	23		
Tamoxifen		0.66	0.25
YES	20		
NO	20		
RT volume		0.07	0.25
Local RT	8		
Loco-regional RT	32		
Ipsilateral lung V20 (Group 1)		0.25	0.73
<20	7		
≥20	33		
Ipsilateral lung V20 (Group 2)		0.74	0.73
<25	19		
≥25	21		
Ipsilateral lung V20 (Group 3)		0.61	0.01
<30	36		
≥30	4		

FVC: Values of forced vital capacity; FEV1: Forced expiratory volume in first second.

Discussion

One of the primary concerns for breast cancer RT is the issue of pulmonary toxicity. Data related pulmonary toxicity has been obtained mostly from studies on lung cancer irradiation because lung exposure is lower in breast irradiation than that in lung cancer. Although it was found strong correlation between RILD and Vdose in lung cancer irradiation, this relationship is smaller in local or loco-regional breast cancer RT.[16] To our knowledge, this is the first study investigating prospectively the acute pulmonary toxicity linked to breast radiotherapy in covantional doses with helical tomotherapy although there are a lot of study[7–9,16–18] including different RT techniques. Van Parijs et al.[7] evaluated pulmonary function of

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Table 5 The characteristics of restrictive and obstructive patients

Patient	Age	RT field	Total MLD	Ipsilateral lung MLD	Ipsilateral lung V5	Ipsilateral lung V20	PFT					
							BeforeRT			At 3 mo. After RT		
							FEV1 (%)	FVC (%)	FEV1 /FVC	FEV1 (%)	FVC (%)	FEV1 /FVC
R1**	58	LR	8.45	11.25	70.31	10.41	84	88	82	73	78	78
R2**	71	LR	12.22	15.22	92.30	27.78	92	88	84	79	76	82
R3**	33	L	10.47	14.92	76.70	22.68	87	85	89	77	69	98
R4*	60	LR	9.54	12.08	73.80	19.50	89	79	93	71	69	84
R5*	44	LR	12.88	15.87	99.0	25.34	57	72	67	52	67	66
R6*	33	LR	14.21	20.52	100.0	33.26	52	58	77	49	48	88
R7*	38	LR	12.07	17.07	99.84	22.75	75	78	101	75	78	101
O1**	60	LR	13.20	13.20	89.91	28.45	96	107	75	78	93	71
O2**	41	LR	10.38	10.38	83.22	23.87	80	93	74	78	91	74
O3**	50	LR^{im}	16.22	16.22	100.0	34.68	96	101	80	71	81	74
O4**	51	LR	12.30	12.30	94.77	24.70	91	97	79	75	81	78
O5*	56	L	9.40	9.40	72.19	15.56	65	86	65	65	86	64

R: Restrictive; O: Obstructive; LR: Loco-regional; L: Local; MLD: Mean lung dose; Vx: Percentage volume of lung receiving ≥x dose. *The patient was restrictive or obstructive at baseline PFTs; **The patient had newly developed restrictive or obstructive lung ingury. ^{im}: Internal mammary nodes were treated additional to whole breast.

patients were treated using HT. They performed total dose 42 Gy in 15 fractions with simultaneous boost as a short course RT but not conventional RT in 50 Gy in HT arm and assessed pulmonary function via FEV1 and diffusing capacity of the lung for carbon monoxide (DLCO) prior to RT and 2 months after completion of RT. In their study, lung toxicity significantly reduced in HT arm according to measurements of DLCO but not FEV1 (p=0.047). We treated 40 patients with breast cancer using HT and found statistically significant reduction in FEV1 and FVC at 3 months after RT (p<0.05). However, in assessment 3 months after RT, restrictive pattern newly developed in 3 patients and obstructive pattern developed in 4 patients based on measurements of PFTs. Except one patient developed restrictive pattern, other obstructive or restrictive patients underwent loco-regional RT. She received concurrent trastuzumab with 50 Gy whole breast and 10 Gy lumpectomy cavity boost RT. The value of ipsilateral lung V20 was 22.68% in this patient and she received concurrent trastuzumab. We found that decrease in FVC at 3 months after RT was significantly more in the patients were given concurrent trastuzumab with RT (p=0.022). The incidence of trastuzumab-induced pneumonitis has been reported in the literature as 0.4–0.6%.[19] Of our patients 97.5% including this restrictive patient had been given taxan-containing regimen although this regimen was not found efficient on PFTs in our study. Paclitaxel cause pneumonitis usually develop 1 week to 3 months after treatment with estimated frequencies of 0.73–12% [20–22]. This suggests to us that new developing restrictive disease may be independent of the lung dose for this patient. One of patients developed obstructive pattern after RT had inner quadrant tumor and multiple high-risk recurrence factors. This patient had also large breast volume (1621.50 cm^3) received adjuvant 50 Gy RT to whole breast and internal mammary nodes on the first three intercostal space and 16 Gy boost to lumpectomy cavity following breast conserving surgery. Therefore, the value of ipsilateral lung V20 was very high with 34.68%. It has been found a correlation between the risk of RP and value of ipsilateral lung V20 in breast cancer irradiation. The incidence of RILD rises up to 7.5–11.5% if the value of ipsilateral lung receiving 20 Gy increase to 20–30%.[18,23,24] Similarly, we found that in the group (n=4) with the value of ipsilateral lung V20 ≥30%, decrease in FVC at 3 months after RT was more (p= 0.019). In our study, in one patient (Table 5, R1**), value of ipsilateral lung V20 was very low with 10.41%. She was Her2 (-) and smoker unlike other restrictive or obstructive patients but she developed newly mild restrictive pattern with minimal reduction in baseline FEV1/FVC. The smoking has been found related to lower incidence of RILD. [25] Ten patients were smoker in our study and only one of them developed restrictive pattern after RT. This finding supports positive effect of smoking on RP.

There are some limitations of this study. First, this study was performed with a single measurement tool to assess the pulmonary function; additionally to PFTs, we may be use DLCO that reflect properties of alveolar-capillary membrane. Second, we present preliminary results of our study. Thus, we cannot comment on long-term effects. However, our study will continue to assess late effects of breast irradiation with helical tomotherapy. Third, the characteristics such as stage and surgery of patients including in this study were heterogeneous. Thus, irradiated volumes were heterogeneous. Finally, the number of patients recruited was too small to allow drawing generalizations.

HT plans provide excellent conformity and homogeneity even in target volumes including lymph nodes in breast cancer irradiations. In very few patients, minimal changes in PFTs can be seen in the acute phase after RT with HT and these changes result in mild restrictive and obstructive pattern. Nevertheless, when considered the risk to benefit ratio, HT can be a viable option for breast cancer patients with complex volumes.

Disclosure Statement

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Overview of Survival and Related Parameters in Malignancies with Brain Metastasis

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OBJECTIVE

Brain metastasis is the most common type of brain tumor. The present study is an investigation of prognostic factors for survival in patients with brain metastasis.

METHODS

We retrospectively investigated patients with brain metastasis who were treated at the Cumhuriyet University center for radiation oncology between 2006 and 2014.

RESULTS

The data of 277 patients were analyzed. Age of the patient, performance status, length of time to metastasis, site of primary disease, and performance of metastasectomy were determined to be factors that affect prognosis. Independent prognostic factors were found to be: time to metastasis (hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.52-0.99; p=0.0047), performance status (HR: 1.40; 95% CI: 1.07-1.85; p=0.015), and metastasectomy (HR: 0.54; 95% CI: 0.33-0.89; p=0.017).

CONCLUSION

Survival rate was better in patients with breast cancer, longer time before metastasis, good performance, and those who had undergone metastasectomy. Therapeutic approaches should be planned with consideration that patients exhibiting these characteristics might have more favorable therapeutic outcomes.

Keywords: Brain metastasis; metastasectomy; prognostic factors.

Introduction

Metastatic brain tumors are seen more often than primary brain tumors in cancer cases, and the rate of brain involvement ranges between 20% and 40% in cases of malignancy.[1–5] The brain is most commonly invaded in patients with lung or breast cancer, which account for 50% and 15–20% of metastatic brain tumors, respectively. Survival remains poor in patients with brain metastasis, and various prognostic scales can be used to make decisions about treatment.[6–9] However, the optimal treatment of brain metastasis is a matter of debate, and many factors can affect the outcome, with each treatment modality having both risks and benefits.[10] Whole-brain irradiation, surgery, and radiosurgery are common modalities for the treatment of brain tumors, and each are recommended by several

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guidelines.[11–13] Overall, local control of the primary disease, and the number, site, and size of the metastasis in the brain must be taken into consideration in the prognostic and therapeutic approaches.

Although current advances in visualization techniques have, in parallel, led to earlier diagnoses and better local treatments of cancer, patient survival is still an important problem. However, the quality of life and survival of the patients have improved, to some extent, with improvements in oncological treatments.[14]

In this study, we investigated the clinical and demographic prognostic factors that affect the survival of cancer patients with brain metastasis. In addition, we aimed to identify any possible independent predictors related to overall survival.

Materials and Methods

For this research, we retrospectively investigated the data of 285 patients with brain metastasis who had been treated in the Radiation Oncology Clinic in the School of Medicine at Cumhuriyet University between 2006 and 2014. The demographic, clinical, and histopathological data of the patients, including the age, gender, metastasis, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status, metastatic organ, second series of irradiation, and history of metastasectomy, were obtained from the patient files and hospital records. Telephone calls were made to determine if the patients were still alive, and these data were also recorded. A total of 8 patients were excluded from the study; of these, 7 had multiple metastases and uncontrolled extracranial metastases, while one had no available data. The performance status was evaluated using the ECOG scoring system.

The statistical analysis was performed using the SPSS statistical software (version 15.0), and the rate of survival was calculated using the Kaplan-Meier analysis. The duration of overall survival covered the time from the date of the diagnosis of brain metastasis until death or the date of the last control. Moreover, a multivariate analysis (Cox Regression Analysis) was performed to evaluate the independent factors that affect survival. Those variables found to be significant in the univariate analysis were evaluated using the multivariate analysis, and a p value of less than 0.05 was considered to be statistically significant. Consent from the Cumhuriyet University School of Medicine Ethical Committee was received prior to the study, with regard to collecting, evaluating, analyzing, and interpreting the data.

Results

For this study, we investigated a total of 277 patients who presented at our clinic with brain metastasis, including 176 (64%) males and 101 (36%) females. The median age of the patients was 59 years old (18–81 years old). The patients were investigated in two groups, those 50 years old or older (220 patients, 79%) and those younger than 50 years old (57 patients, 21%).

The primary diagnoses of the patients were: 162 cases of lung cancer (58%), 57 cases of breast cancer (21%), 17 cases of gastrointestinal system cancer (6%), 14 cancer patients with unidentified primary sites (5%), 12 cases of genitourinary system cancer (4%), 8 cases of gynecological cancer (3%), and 7 cases of other types of cancer (3%).

All of the patients had undergone total cranial irradiation, in which three-dimensional conformal radiotherapy was applied using a Varian DHX Eclipse planning system. The radiotherapy was applied at a dose of 3000 cGy, with 300 cGy/day for the total cranial area. Other treatments were also applied for the brain metastasis, with 30 patients (11%) having undergone metastasectomies. A second series of irradiation was required in 21 patients (8%), due to progression, and cranial conformal radiotherapy was applied as the second serial irradiation. This protocol was conducted at a total of 2000 cGy, with 200 cGy/day for the cranial area. Stereotactic radiosurgery (SRS) was not applied in any of the patients.

Overall, the median survival was determined to be 3 months (1–98 months), the mean duration of survival was 7.6±0.68 months, and the median value of the time to metastasis was 11 months (1–119 months).

Based on the univariate analysis, the prognostic factors which affected survival included the site of the primary disease (breast cancer, p=0.035), age of the patient (<50 years old vs ≥50 years old, p=0.033), performance status of the patient (p=0.005), history of metastasectomy (p=0.006), and time for the development of metastasis (p=0.055). However, the gender, comorbidity, metastasis at diagnosis, and second series of radiotherapy (RT) were not determined to affect survival (p>0.05). Table 1 shows the prognostic factors that affect survival. In addition, the survival curves with regard to primary disease are demonstrated in Figure 1, with regard to the ECOG performance status in Figure 2, and with regard to the application of metastasectomy in Figure 3.

Those independent prognostic factors which positively affect survival were found to be: a favorable

Table 1 Univariate analyses of subgroups in accordance to the values of median survival

Prognostic factors	Number of patients (%)		Median survival[1]	P
	n	%		
Gender				
Female	101	36	5	0.088
Male	176	64	3	
Age				
<50 years	57	21	7	**0.033**
≥50 years	220	79		
Comorbidity				
No	190	69	4	0.291
Yes	87	31	3	
Primary disease				
Lung	162	58	3	**0.035**
Breast	57	21	7	
Other	44	16	2	
Unknown primary origin	14	5	3	
Duration of the metastasis development				
≤18 months	207	75	3	0.055
>18 months	70	25	5	
Metastasis at initial diagnosis				
No			4	0.763
Yes			3	
ECOG performance status				
ECOG 0–1	147	58	6	**0.005**
ECOG 2–4	107	42	2	
Number of metastatic sites				
Isolated brain metastasis	112	40	4	0.816
Multiple organ metastasis	165	60	3	
Metastasectomy				
No	247	89	3	**0.006**
Yes	30	11	12	
Second serial radiotherapy				
No	256	92	3	0.210
Yes	21	8	11	

[1]Median Survival: Median survival following the development of metastasis. ECOG: Eastern Cooperative Oncology Group.

ECOG performance status (HR=1.40, 95% CI=1.07–1.85; p=0.015), the application of metastasectomy (HR=0.54, 95% CI=0.33–0.89; p=0.017), and time to metastasis of greater than 18 months (HR=0.72, 95% CI=0.52–0.99; p=0.047). The independent prognostic factors, as determined via the multivariate analysis, are illustrated in Table 2.

Discussion

In this retrospective study, we investigated the prognostic factors that affect survival in patients with solid tumors and brain metastasis. In these cases, there is often a poor prognosis and low survival rate if the patient is not treated.[15]

Certain important prognostic factors can be used to assess the therapeutic approach towards patients with brain metastasis. In three studies conducted by the Radiation Therapy Oncology Group (RTOG), a total of 1.200 patients were analyzed to determine the prognostic factors in brain metastasis, by evaluating whole brain radiotherapy with different fraction-dose schedules. In this analysis, the age, performance status, control of the primary tumor, and presence or absence of extracranial metastasis were determined to be important prognostic factors. As a result of the analysis,

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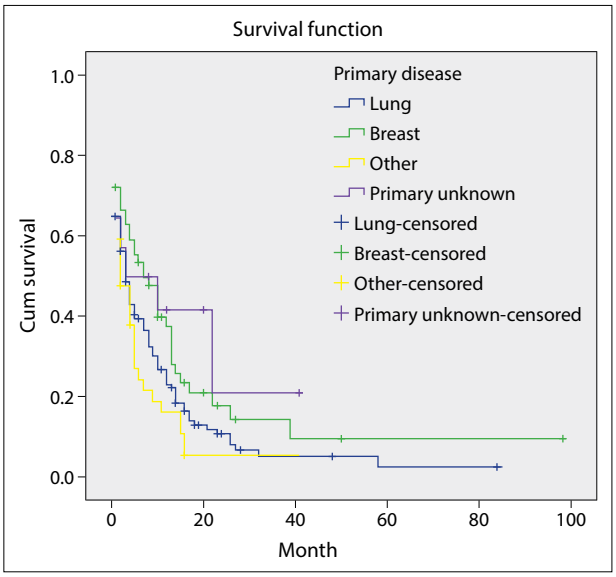

Fig. 1. Survival curves in regard to the primary disease.

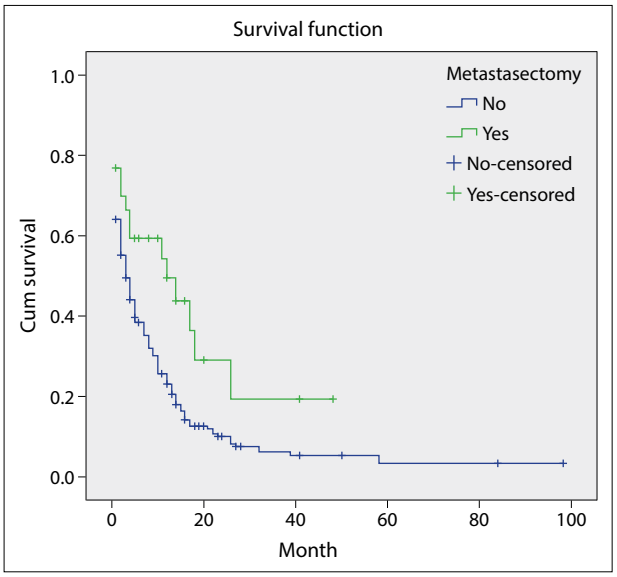

Fig. 3. Survival curves in regard to the application of metastasectomy.

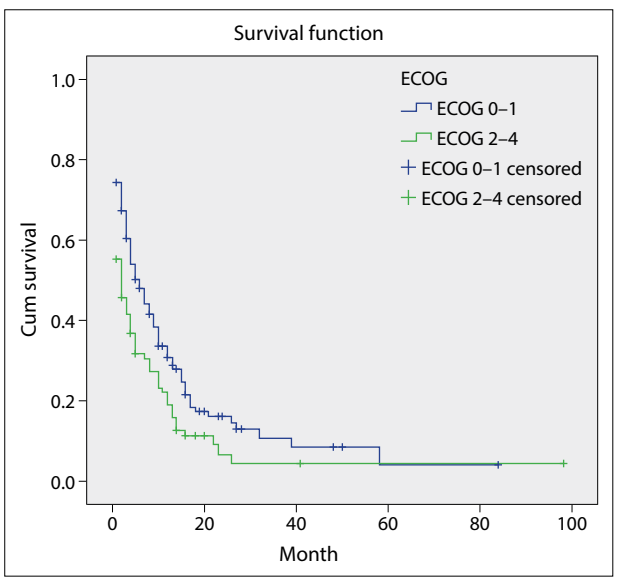

Fig. 2. Survival curves in regard to the ECOG performance status.

three prognostic classes were determined and defined as the recursive partitioning analysis (RPA), including RPA classes I, II, and III:[16,17]

1. Class I: patients younger than 65 years old with brain metastasis only, and with the lower Karnofsky Performance Status (KPS) of 70.
2. Class II: those patients not included in RPA classes I and III.
3. Class III: patients with a KPS of less than 70.

The best survival was found in RPA class I, with a median value of 7.1 months, while the worst was in RPA class III, with a median value of 2.3 months. The median value of survival was 4.2 months in RPA class II.[16] In a retrospective study by Nieder et al., including those patients younger than 50 years old with brain metastasis, the prognostic factors that affected survival were the performance status, number of metastases in the brain, presence of extracranial metastasis, gender, and primary disease of the breast.[18] In the same study, the time to metastasis was found to be another factor that affected survival in those patients over 50 years old [18]. In the present study, the survival rate was found to be statistically significantly better in patients younger than 50 years old (7 months vs 3 months).

The Eastern Cooperative Oncology Group (ECOG) performance status is used widely in oncology to assess a patient's state of performance. This performance status has been reported in the literature as an efficient and preferable prognostic factor for metastatic tumors.[19] In our study, we determined that those patients with ECOGs from 0–1 were 1.4-fold more likely to survive than those with ECOGs from 2–4. However, the presence of extracranial metastasis was not found to be statistically significant with regard to survival.

Some studies have reported that the site of the primary tumor is another important prognostic factor that affects overall survival.[18,20] In some of these studies, the rates of survival were reported to be higher in those patients with breast cancer, when compared to other types of cancer.[18,20,21] For example, Nieder et al. performed a study including patients younger than

Table 2 Multivariate analyses of subgroups (ECOG performance status, metastasectomy and duration of the metastasis development)

Prognostic factors	Hazard ratio	95% CI	p
Duration of the metastasis development			
≤18 months	1		
>18 months	0.72	0.52–0.99	0.047
ECOG performance status			
ECOG 0–1	1		
ECOG 2–4	1.40	1.07–1.85	0.015
Metastasectomy			
No	1		
Yes	0.54	0.33–0.89	0.017

ECOG: Eastern Cooperative Oncology Group; CI: Confidence interval.

50 years old with brain metastasis, and the median survival was 8.5 months in patients with primary breast cancer, but only 6 months in other types of cancer.[18] In the same study, survival was also found to be better in those patients with primary breast cancer who were over 50 years old. However the diagnosis of primary breast cancer was not found to be significant in either age group in the multivariate analysis. Similarly, we determined that the values of median survival were 7 months in patients with breast cancer and brain metastasis, 3 months in lung cancer with brain metastasis, 3 months in brain metastasis with an unidentified primary site, and 2 months in the other metastatic cancer types.

Additional studies in the literature have reported that the time from the initial diagnosis to brain metastasis is closely related with the prognosis.[22] Duransoy et al. evaluated the prognostic factors following metastasectomy in 62 patients with brain metastasis, and although it was not statistically significant, better survival was reported in the patients with times to metastasis longer than 12 months (10 months vs 6 months).[22] Nieder et al. found the rate of survival to be significantly higher in patients over 50 years old who developed brain metastasis over a period longer than 12 months.[18] In the present study, a survival advantage was present in those patients who developed brain metastasis over periods longer than 18 months. However, the group with the 12-month stratification did not show a survival advantage.

Metastasectomy is another factor which determines a patient's prognosis, and the duration of survival has been reported to be quite long in those patients that underwent metastasectomies.[23,24] Moreover, those cases undergoing surgical treatment had longer durations of survival, which was statistically significant. Early randomized studies have demonstrated that patients with solitary brain metastasis benefit from aggressive local therapy.[25–27] In a serial study by Ferrara et al. that included 100 patients with solitary brain metastasis, the total duration of survival following metastasectomy was found to be 10.2 months.[28] Duransoy et al. have reported the total duration of survival as 9 months, and the median duration of survival as 6 months in 62 patients who underwent metastasectomy. In our study, the median survival time was 12 months in those patients with histories of metastasectomies, but it was 3 months in those who could not undergo metastasectomies. This result suggests that metastasectomy is an independent prognostic factor in patients with brain metastasis.[22]

The application of whole brain irradiation following surgical intervention is still a matter of debate; however, all of our patients underwent cranial radiotherapy following surgery, so we could not make an interpretation of this issue. In the study by Duransoy et al., the duration of survival was 13 months in those patients undergoing post-operative RT, but it was 5 months in those patients who did not undergo post-operative RT ($p<0.001$). Therefore, we believe that the application of cranial radiotherapy following surgery is a better approach.

Conclusion

This study revealed that the time to metastasis, history of metastasectomy, and ECOG performance status are factors that affect survival in patients with brain metastasis. However, one must keep in mind that the treatment of brain metastasis must be considered more

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carefully in patients with breast cancer, patients younger than 50 years old, and in those cases of late metastasis and good performance.

Limitations

This research had some important limitations; for example, it was a retrospective study with a limited amount of data for analysis. Therefore, these findings should be confirmed with prospective controlled randomized trials. The second limitation was related to sample size, since our data was based on a relatively small study population and involved records from a single center. Larger cohort studies would be beneficial in obtaining stronger statistical results. Finally, this research did not include any patients who underwent stereotaxic RT. Therefore, we suggest that further studies which include cases of the same primary disease (e.g. breast cancer), and that also include a sufficient number of cases undergoing metastasectomy and stereotaxic RT would make important contributions to the literature.

Disclosure Statement

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Investigation of The Physical and Functional Needs in Adult Cancer Patients Consulted to Physiotherapy and Rehabilitation

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OBJECTIVE

The purpose of this study was to investigate the physical and functional needs of hospitalized cancer patients consulted to physiotherapy and rehabilitation services.

METHODS

Total of 176 patients with various cancer diagnoses who were treated at Hacettepe University Oncology Hospital and were consulted to physiotherapy and rehabilitation were included in this retrospective study. Patient data regarding diagnosis, metastasis condition, and treatment types, as well as rehabilitation needs such as performance of daily life activities, physical function deficiencies, and sensory-perception problems were evaluated and recorded by physiotherapists.

RESULTS

Average age of the 87 male and 89 female patients included in this study was 56.25±14.53 years. According to evaluations of performance of daily life activities, 137 (77.8%) of the participants had difficulty with mobility, 132 (75%) had difficulty with transfer activities, and 106 (60.2%) had difficulty using the bathroom. It was observed that 162 (92%) of the patients experienced deconditioning, 150 (85.2%) had fatigue, and 149 (84.7%) had balance problems. In addition, 42 (24.4%) of the patients had sensory problems.

CONCLUSION

It is important to point out that cancer patients have various forms of rehabilitation needs, including functional deficiency, dependency in daily life activities, and sensory-perception-cognitive problems.

Keywords: Cancer; physiotherapy; rehabilitation.

Introduction

As the survival from cancer increases in the world and in our country, the chronic conditions caused by the disease have gained importance, making rehabilitation programs an important part of the treatment in order to maximize the functional level to the highest and to increase the quality of life.[1]

After being diagnosed with cancer, patients, families and caregivers make great efforts to cope up with the problems that emerge due to the disease and treatments. Patients' performance in their daily life, their ability to continue their profession or education, and their participation in family and social activities are adversely affected due to the progressive nature of the

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disease, as well as the side effects of applications such as chemotherapy and radiotherapy.[2]

In 1978, for the first time, Lehman et al. investigated the rehabilitation needs of 800 cancer patients and reported that their most prominent problems were the ones related to psychological stress, pain, muscle weakness, daily living activities, ambulance and family support.[3]

Emotional support, pain, difficulties in daily living activities, and mobility problems were reported by DePompolo in 1994; standing up from a chair, using the toilet, showering, walking and climbing the stairs were amongst the problems reported by Sabers in 1999; and sleeping disorders, pain, fatigue and anxiety were the problems stated by Whelan in 1997.[4–6]

In 1998, however, Van Harten pointed out that rehabilitation problems included not only physical function adversities but also psychosocial and cognitive function difficulties, and that several of these problems can be seen together.[7]

In fact, oncologic rehabilitation differs from rehabilitation programs for other diseases in some aspects. Here, physiotherapists treat their cancer patients with more flexible and differentiated treatment programs that take into account changes in their conditions resulting from both the disease and treatments. For example, daily exercise program varies depending on the level of fatigue and factors affecting it (blood table, chemotherapy session, etc.). Hence, it is important that the cancer patients are evaluated in detail, their needs are identified and any changes in their conditions are detected immediately.

Taking these into account, the purpose of our study was to determine physiotherapy and rehabilitation needs of cancer patients who are hospitalized due to complications or some treatment procedures, and to help physiotherapists to establish an appropriate physiotherapy and rehabilitation program that meets all the needs of their cancer patients.

Material and Methods

Our study included cancer patients hospitalized at Hacettepe University Oncology Hospital between 2011 and 2015. For all participants physiotherapy and rehabilitation consultation was requested by the oncologist. In this retrospective, single-center, cross-sectional study, adult patients with different cancer diagnoses were included. Ethics committee approval for this study was obtained from Hacettepe University, Non-Interventional Ethics Committee, No. GO 16/158–30.

Table 1 Evaluation of physical functions

Pain
Visual analog scale
Fatigue
Visual analog scale
Joint range of motion
Goniometric measurement
Muscle strength
Manuel
Hand dynamometer
Sensory
Superficial sensation
Foot plantar pressure sensation
Polyneuropathy
Edema
Measuring tape
Balance
Standing eyes open/eyes closed
Sitting eyes open/eyes closed
Respiration
Chest circumference measurement
Frequency

Minimum one week of hospitalization, ability to communicate, being in the II-IV stage of the illness, and being in the age range of 18–65 years were the inclusion criteria. Patients who did not want to participate in the physiotherapy and rehabilitation program were excluded from the study.

Medical records of the participants were precisely checked and their physiotherapy-rehabilitation needs were evaluated in accordance with their diagnosis, anamnesis and major complaints. Along with recording the patients' diagnoses, demographic data, metastatic status, and their treatment, the participants' daily life activities (such as transfer, mobility, self-care and dressing), physical functional deficits (such as pain, fatigue, deconditioning, and balance problems) and their sensory-perceptual problems (such as sensory loss, polyneuropathy, cognitive and communication problems) were also evaluated and recorded by physiotherapists. The evaluation of physical functions is shown in Table 1.

Statistical Analysis

SPSS 10.0 package program was used for the analysis. Measurable data is expressed as arithmetic mean, ± standard deviation.

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Results

176 cancer patients were included in the study, out of whom 89 (50.6%) were female and 87 (49.4%) were male; the average age was 56.25±14.536 years.

Distribution of diagnosis of the individuals, which is shown in Table 2, reveals that lymphoma (20.5%), breast cancer (15.3%) and multiple myeloma (10.8%) were the most common diagnosis.

Reasons for admission to the hospital are shown in Table 3, according to which patients were frequently admitted to the hospital for diagnostic and/or therapeutic purposes. Metastasis was recorded in 100 (58.5%) of the individuals. Chemotherapy was applied in 49 (29.7%), radiotherapy in 11 (6.7%), radiotherapy and chemotherapy in 13 (7.9%), and other treatments in 92 (55.8%) of the participants. The distribution of patients according to their treatment procedures is given in Table 4.

When individuals' physiotherapy and rehabilitation needs were assessed, it was determined that deconditioning, fatigue, balance problems, transfer and mobility difficulties were the most common and primary ones. In DLA, it was observed that patients had the most problems with mobility and transfers. Physiotherapy and rehabilitation needs of patients are categorized and their distributions are shown in Table 5, 6 and 7.

Table 2 Diagnosis distributions

Cancer type	n	%
Lymphoma	36	20.5
Breast cancer	27	15.3
Multiple myeloma	19	10.8
Lung cancer	16	9.1
Leukemia	13	7.4
Brain tumors	13	7.4
Colon cancer	7	4.0
Gastric cancer	7	4.0
Pancreatic cancer	7	4.0
Kidney cancer	6	3.4
Ovarium cancer	4	2.3
Liver cancer	3	1.7
Prostate cancer	3	1.7
Nasopharyngeal cancer	2	1.1
Larynx cancer	2	1.1
Endometrium cancer	2	1.1
Duodenum cancer	2	1.1
Adenoma	1	0.6
Bladder cancer	1	0.6
Esophageal cancer	1	0.6
Uterus cancer	1	0.6
Thymoma	1	0.6

Table 3 Reasons of hospitalization

	n	%
Diagnostic and therapeutic purposes	45	25.5
Deterioration in general health status	36	20.4
Inability to walk and/or loss of force	30	17
Respiratory problems	16	9
Pain	13	7.3
Infection	12	6.8
Cytopenia	7	3.9
Palliative care	6	3.4
Fatigue	4	2.2
Other	7	3.9

Table 4 Treatment status of the patients

Ongoing treatments	n	%
Chemotherapy	49	29.7
Radiotherapy	11	6.7
Chemotherapy and radiotherapy	13	7.9
Other	92	55.8

Table 5 Needs in daily living activities

Needs in daily living activities	n	%
Mobility	137	77.8
Transfer	132	75.0
Using the bathroom	106	60.2
Dressing	75	42.6
Self care	63	35.8
Eating	49	27.8

Table 6 Requirements for physical problems

Physical problems/needs	n	%
Deconditioning	162	92.0
Fatigue	150	85.2
Balance problems	149	84.7
Pain	113	64.2
Edema	58	33.0
Limitation	49	27.8
Respiratory problems	49	27.8
Swallowing problems	12	6.8
Decubitus ulcers	9	5.1
Lymphedema	7	4.0

Table 7 Sensory, perception and cognitive problems

Sensory-perception problems	n	%
Sensory problems	63	35.8
Cognitive problems	20	11.4
Communication problems	20	11.4

Discussion

Results of our retrospective study, where cancer patients who were hospitalized due to complications or some treatment applications were evaluated in terms of their physiotherapy and rehabilitation needs revealed that daily living activities such as mobility, transfer and using the bathroom, as well as physical problems such as deconditioning, fatigue, balance problems, and pain were the most common complaints of the patients. Furthermore, polyneuropathy was found to be the most common sensory problem.

According to the results of the study in Switzerland by Ture et al. out of all cancer patients who were rehabilitated, the ones with digestive system tumors were the first, the patients with thoracic tumors were the second, and the ones with breast cancer were the third group who had benefitted from the rehabilitation program the most.[8] Moreover, male patients were reported to be less rehabilitated than female patients.

In the present study, diagnosis distribution of 176 cancer patients who required physiotherapy and rehabilitation consultation was reported in the following order: lymphoma, breast cancer, multiple myeloma, lung cancer, leukemia, and brain tumors. In our study, the need for rehabilitation was found to be equally important for both male and female patients. Metastasis was recorded in 58.5% of the patients participating in the study. This indicates that the diagnosis distributions of patients who require physiotherapy and rehabilitation consultation vary significantly and their illness is in an advanced stage.

Mavsas et al. investigated functional disorders and rehabilitation needs of 55 patients in the medical oncology unit and highlighted many previously unknown rehabilitation requirements of the patients; the most primary one of which was deconditioning.[1]

Aras et al. investigated rehabilitation needs of 300 in-patients of the oncology hospital who did not apparently require any physiotherapy and rehabilitation.[9] Results of the study showed that 245 (81.7%) of the participants were actually in need of rehabilitation mostly due to fatigue, deconditioning, difficulties in daily living activities, ambulation problems, and pain. In addition, they also stated that joint contracture and lymphedema in patients with breast cancer, transfer problems in patients with lung cancer, and joint contractures in patients with bone cancers are more frequent. It was also reported that out of 245 patients who were identified as the ones in need of rehabilitation, only 2 were consulted to physiotherapy and rehabilitation unit.

In their study examining functional impairments and rehabilitation needs of non-operated lung cancer patients, Bayly et al. reported that fatigue, respiratory distress and pain are the most important issues to be considered in the rehabilitation program.[10]

In our study, evaluation of the patients' daily living activities showed the loss of independency in 77.8% of the patients in terms of mobility, in 75% in terms of transfer activities, and in 60% in terms of using the bathroom. In our patient group, for which physiotherapy and rehabilitation needs were identified by the oncologist, it was noticed that difficulties in mobility and transfer activities were very common, and that elevated levels of dependency during daily living activities was the reason for requesting physiotherapy and rehabilitation consultation.

Rehabilitation needs of the patients in accordance with their physical problems were determined as: 92% deconditioning, 85.2% fatigue, 84.7% balance disorders, and 64.2% pain. Similar to the literature, we also concluded that deconditioning and fatigue were the most prominent problems of the patients within the physiotherapy and rehabilitation program. Moreover, edema/lymphedema, joint motion limitations, respiratory problems and swallowing problems were also determined depending on the diagnosis and involvement zone. Hence, deconditioning and fatigue leading to deficits in balance, mobility and transfers were among the first clues that would cause physicians to consult physiotherapy and rehabilitation unit. Patients suffering excessive fatigue and ambulatory loss are seen to be the primary candidates for physiotherapy and rehabilitation consultation.

Gültekin et al. examined health care expectations of 40 lung patients.[11] According to the results, patients expect physicians to "cease the pain", nurses to "relieve pain and discomfort", psychologists to "reduce their sadness and grief", dietitians to "prevent weight loss", physiotherapists to "eliminate muscle weakness", and social workers to "help them maintain good relationships with others". This suggests that patients need a multidisciplinary team to tackle and cope with their problems.

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The rehabilitation needs we have shown in our work show that physiotherapists, as an important member of the multidisciplinary team, are needed for the treatment and follow-up of cancer patients.

The researchers also concluded that functional malfunctions of cancer patients are not adequately and precisely identified, appropriate and timely physiotherapy and rehabilitation consultations are generally underestimated, and family members are not trained and informed about rehabilitation needs of the patients. In addition, in the study investigating and comparing the needs of cancer patients in admission to and discharge from the hospital; it was emphasized that the rehabilitation needs of the patients were continued at discharge and that they should be followed up with home programs.[1]

Conclusion

The present study showed that high levels of dependency in daily living activities and major problems in physical functions identified in cancer patients with physiotherapy and rehabilitation consultation is an indication of the lack of knowledge of health professionals in this area. Problems identified in cancer patients are related to each other and they generally continue for a certain period of time; that's why it is believed that training patients and their families, as well as health professionals on physiotherapy and rehabilitation in cancer can be a solution to overcome these deficiencies.

Disclosure Statement

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CASE REPORT

Leptomeningeal Carcinomatosis in a Krukenberg Tumor Associated with Signet Ring Cell Gastric Cancer

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SUMMARY

Leptomeningeal carcinomatosis (LCM) is a rare complication of gastric cancer. It usually occurs late in advanced stage of disease and is sometimes misdiagnosed as toxicity of chemotherapeutic agents. Here we report a rare case of gastric cancer that developed LCM in follow-up. A 28-year-old woman with signet ring cell gastric cancer associated with Krukenberg tumor was admitted with persistent headache, nausea, vomiting, vertigo, and diplopia. Linear appearance of contrast enhancement in cerebellar fissures and around cranial nerves was seen in magnetic resonance imaging and cerebrospinal fluid was hypercellular with numerous carcinoma cells. LMC was confirmed and treated with intrathecal methotrexate and additional whole-brain irradiation. LCM is a rare complication, but occurs more often than expected and is often misdiagnosed. If patient who is being treated for gastric cancer presents with neurological symptoms, LCM should be kept in mind. Clinical improvement can be achieved with current treatment modalities, including radiotherapy, chemotherapy, or targeted molecules.

Keywords: Gastric cancer; Krukenberg tumor; leptomeningeal carcinomatosis; signet ring cell.

Introduction

Leptomeningeal carcinomatosis (LMC), also known as leptomeningeal metastases, is a clinically important and severe complication in patients with cancer and defined as diffuse spreading of malignant cells throughout the arachnoid membrane and the pia mater by propagation in the cerebrospinal fluid (CSF).[1]

It is associated with major neurologic symptoms and disability such as headache, nausea, vomiting, backache, radiculopathies, cranial nerve palsies, mental change and high mortality.[2,3] It can be observed in 3–8% of all cancer patients, and diagnosed in 1–5% of patients with solid tumors.[2,3] Although it may occur with virtually any malignancy, adenocarcinoma is the most common form of LMC and is most commonly seen in patients with breast cancer, lung cancer- particularly small cell, also leukemia and lymphoma.[4,5] LMC is thought to be relatively rare in gastric cancer, with a frequency of 0.16–0.69% in all gastric cancer patients.[6,7]

Here we report a rare case of signet ring cell gastric cancer associated with Krukenberg tumor developed LMC in follow-up who was treated with concurrent radiotherapy and chemotherapy.

Case Report

A 28-year-old woman was admitted with persistent headache, nausea, vomiting, vertigo and diplopia. Her complains had lasted approximately for 30 days and became more apparent last week.

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In patient's medical history, it's learned that she was diagnosed as signet ring cell gastric cancer 22 months ago and total gastrectomy was performed. 6 cycles of 5-fluorouracil (5-FU)/folic acid and 45 Gy of radiotherapy was administered in follow.

14 months later from the diagnose date, 17 cm right ovarian mass detected in her routine follow-up and she had a surgery of right salpingo-oophorectomy. She was diagnosed as Krukenberg tumor and 6 cycles of docetaxel, cisplatin, and 5-FU (DCF) chemotherapy was planned but due to the side effects of the therapy she was discontinued her therapy after the first cycle.

In her physical examination her weight was 52 kg and height was 173 cm. She was oriented to time, place and person. Her vital signs were as follows: a blood pressure of 110/70 mmHg, a pulse rate of 88 beats/min and a respiration rate of 17 breaths/min. She had neck stiffness but doesn't have fever or skin rash. She had temporary spontaneous nystagmus and dysarthria. Psychomotor slowing was detected as a sign of an alteration on her mental status. Both lower extremities had paresis with preserved deep tendon reflexes. Plantar responses were flexor. Sensory examinations were normal. Hepatosplenomegaly was not noted.

In her laboratory tests no abnormality was detected except low hemoglobin levels of 9,6 g/dL (10.7–13.0 g/dL) and highly CA 19–9 levels, elevated from 156.6 U/ml to 1901.6 U/ml (0–35 U/ml) within 3 months.

Magnetic resonance imaging (MRI) study of brain with intravenous contrast was performed. Linear appearance of contrast enhancement was shown in cerebellar fissures and around cranial nerves.

A lumbar puncture and analysis of the cerebrospinal fluid (CSF) was performed. Gram stain and culture were negative. The results showed an elevated protein concentration with normal glucose content and hyper cellularity with many malignant cells.

Radiological diagnosis of LMC was confirmed through the results and the patient was treated with intrathecal administration of 15 mg methotrexate, once a week, for 3 times. Additional whole-brain irradiation of 20 Gy in daily fractions was performed.

By the therapy she had dramatic relief from headaches, nausea, vomiting and diplopia. She became enable to feed orally and was discharged after had been planned DCF systemic chemotherapy of 6 cycles.

Discussion

LMC is very rare complication of gastric cancer, occurring in 0.16–0.69% of all gastric cancer patients. [6,7] However, recent studies showed that frequency of LCM is might be more often than known before. Emoto and colleagues[8] reported that 5.6% of patients with peritoneal metastasis of gastric cancer developed LCM during the course of therapy.

Breast cancer, melanoma and lung cancer are the most common solid tumors associated to LCM.[4,5] However, Lee et al.[6] reported that gastric cancer was most common solid tumor to metastasize to the meninges, accounting for 33%, followed by lung cancer (31%), and breast cancer (26%).

The neurological symptoms of LMC are sometimes misdiagnosed as the toxicity of chemotherapeutic agents. We recommend scanning for LMC for patients with neurological symptoms that occurred during treatment. Recent studies suggest that the standard tool for imaging LMC is Gadolinium –enhanced MRI[9] and also cytology of the CSF is the gold standard for LMC cancer diagnosis, although false-negative results have often been reported.[10] That a combination of enhanced MRI and CSF cytology be used for accurate diagnosis of LMC.[10] Although MRI is generally regarded as superior to CT for the diagnosis of LMD, factors such as cost, availability and patient convenience often dictate that contrast-enhanced CT scans are the first studies ordered for the patient with suspected LMD, especially in the acute clinical setting when hydrocephalus should be excluded prior to lumbar puncture.[11]

The prognosis of LMD is unpromising without treatment, with an average survival of 6 weeks following diagnosis.[12] With treatment, the average survival is 4 to 6 months[4] with survival tending to be longer in patients with breast cancer or hematologic malignancies.

The goals of treatment include prolonging survival, improve neurologic function if not possible palliating symptoms. Intrathecal (IT) chemotherapy using MTX, cytosine arabinoside (Ara-C), and thiotepa is the mainstay of the treatment of LMC,[11] though the efficacy and superiority to systemic chemotherapy of this regimen is still unclear. A recent study shows that combination of MTX, Ara-C and hydrocortisone found more effective than the administration of MTX alone in LCM associated with solid tumors.[13] A standard induction therapy 10 mg twice a week for four weeks. If there is no response, additional four-week induction therapy or an alternative approach may be considered.[14] Recently systemic administration of targeted therapies in selected patients with LMC resulted in clinical benefit as example erlotinib and alectinib in lung cancer.[15,16] However large-scale clinical studies are required for

standardizing intrathecal chemotherapy. On the other hand, Radiation therapy (RT) appears to be more effective at relieving symptoms than does (IT) chemotherapy for symptoms caused by localized leptomeningeal metastases. Also whole-brain radiation is often performed for LMC patients to palliate their symptoms, decrease bulky disease, and correct CSF flow abnormalities.[8] 30–36 Gy in 3 Gy daily fractions is recommended by several studies.[17,18] CSF drainage is also performed to relieve the symptoms of elevated intracranial pressure.[19] Corticosteroids is rarely effective in neurological deficits but can improve headaches better than analgesics. Furthermore, anticonvulsants should not be used as prophylactic and reserved for patients with seizures. Emoto and colleagues[8] reported that in patients with poor prognostic factors such as poor performance status or MRI-proven LMC, palliative therapy may be the most suitable treatment strategy. In addition, the clinical efficacy of IT MTX in conjunction with RT is illustrated by several study.[20,21]

In summary, LCM is a rare complication of gastric cancer but recent studies imply that it occurs more than expected but usually might be misdiagnosed. Cytology of the CSF is the gold standard although to avoid from false-negative results, combination of enhanced MRI and CSF cytology be used for accurate diagnosis. Prognosis is poor and worsened if not treated. But, clinical studies are required for standardizing therapy. In conclusion, if the patient who treated for the gastric cancer presenting with neurological symptoms, should be excluded for LCM by clinician.

Disclosure Statement

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REVIEW

Allogenic Stem Cell Transplantation and Total Body Irradiation

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SUMMARY

The clinical importance of bone marrow transplantation has increased considerably in recent decades. More than 450 centers for bone marrow transplantation now exist worldwide, performing more than 5000 transplantations per year. The number of transplant centers and patients has increased dramatically in Turkey in the last several years. When transplant donor and recipient are different individuals, hematopoietic graft is known as allogeneic graft. Total body irradiation (TBI) remains an important component of allogeneic hematopoietic stem cell transplant, with the goal of eradicating residual malignant cells and modulating the immune system of the transplant recipient. TBI is especially advantageous in allogeneic stem cell transplantation, since its biological effects can be exerted uniformly without sparing the "sanctuary" sites, such as nervous system or testicles. In this report, the role of TBI in allogeneic stem cell transplantation is reviewed.

Keywords: Allogenic stem cell transplantation; bone marrow donor; total body irradiation.

Allogenic stem cell transplantation involves transferring the stem cells from a healthy person (the donor) to a patient (the recipient) following high-intensity chemotherapy and/or irradiation. The donor can be a relative of the patient or a stranger named as unrelated donor. The important thing is that the donor's immune system markers should closely matched to patients'. To find a HLA –matched sibling donor is not possible for 70% of the patients who need immediately an allogenic hematopoietic stem cell transplant.[1] To overcome this many countries developed regional or national bone marrow databases to find a matching donor. In Turkey the Turkkök Project (National Marrow Donor Program) has developed into a large national organization, allowing access to a large database of unrelated donors, where data of more than one million healthy persons stored. This has resulted increased chance of finding a matching donor for patients of all races/ethnicities. The Turkkök Project has also developed programs and approaches that have successfully increased the efficiency of the search process, which has decreased the waiting time to transplant. It is also expected an increase in the feasibility of allogeneic stem cell transplanation and requirement of total body irradiation (TBI) applications in our country with this project.

Allogeneic Stem Cell Transplantation, using human leukocyte antigen (HLA)-matched sibling or unrelated bone marrow donors has been used successfully to treat patients with high-risk or relapsed hematologic malignancies.[1,2] Some solid tumors are under the investigation of allogeneic transplantation (Table 1). Successful bone marrow transplantation with a combination of cyclophosphamide and total body irradiation as a conditioning regimen was first reported in the 1970s.[3]

TBI is an important component of hematopoietic stem cell transplant with the goal of eradicating residu-

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Table 1 Tumors which allogenic transplantation using with total body irradiation is performed

Standard treatment	Under clinical investigation
Acute lymphoblastic leukemia, (ALL) Acute/chronic myelogenous leukaemia (AML/CML)	Neuroblastoma, Ewing sarcoma, High/low grade non-Hodgkin lymphoma, Multiple myeloma

al malignant cells and modulating the immune system of the transplant recipient. TBI has several advantages over chemotherapy since its biologic effects can be exerted uniformly throughout the body without sparing of the "sanctuary" sites such as the nervous system or testis, which is evident for many chemotherapy drugs. However, there are always concerns with the use of irradiation regarding the long term sequelae, including cataracts, second malignancies, and developmental problems in pediatric cases specifically. Because of these concerns, chemotherapy regimens omitting total body irradiation have been studied extensively where busulfan replaced TBI.[4,5] Both TBI/Cyclophosphamide or Busulfan/Cyclophosphamide regimens have been accepted standard conditioning regimens since the 1980s. There are a few published papers comparing TBI/Cyclophosphamide versus Busulfan/Cyclophosphamide for stem cell transplantion and their long-term results for different leukaemia types (Table 2). In 2010, a meta-analysis compared the clinical results of different conditioning regimens for various leukaemias. In this metaanalysis, different studies were evaluated for therapeutic effects of TBI/CY or BU/CY regimens with assessment of engraftment, relapse patterns, complications, and disease-free survival.[6] A total of 3172 patients from 18 trials have been evaluated and TBI/CY regimen was reported to have similar occurrence of engraftment, acute and chronic graft-versus-host disease with BU/CY, but had higher rates of cataract, interstitial pneumonitis, later growth or developmental problems.[6] BU/CY regimen was related with more severe complications such as veno-occlusive disease of liver, hemorrhagic cystitis, and treatment-related mortality The authors also concluded that different treatment regimens and leukaemia types may affect the complications and outcome.[6] The results of TBI containing regimens in acute lymphoblastic leukemia (ALL) is summarized in Table 2. The ideal conditioning regimen for leukaemia patients undergoing bone marrow transplantation still remains unknown and the results of current ongoing BFM trial will be the answer of this question in the near future.

Table 2 The results of TBI containing regimens in acute lymphoblastic leukemia

Author	Regimen	Overall Survival	
Bunin[5]	BU	67%	
	TBI	47%	3 year
Davies[4]	CY/TBI	55%	
	BU/CY	40%	3 year
Park J[15]	TBI/CY	64.3%	2 year
Kamer –unpublished results	TBI/CY	69%	2 year

BU: Busulfan; CY: Cyclophosphamide; TBI: Total body irradiation.

Numerous different techniques have been developed to deliver TBI.[7–10] The choice of a particular technique varies among institutes and depends onexperience of the institute, the workload of the department, geometry of the treatment room, available infrastructure and equipment, and treatment protocol. In the majority of departments two treatment techniques or combination of both are used in practice. An anteroposterior posteroanterior (AP/PA) technique generally provides a better dose uniformity along the longitudinal body axis, but it is not possible to cover the whole body with a single field and use of multiple neighboring fields is always a challenge. Bilateral TBI (treating from the left and right side of the body) can be more comfortable to the patient if seated on a specially designed TBI Chair (Figure 1) but, presents greater variation in body thickness along the path of the beam. Thus compensators are required to achieve dose uniformity along the body axis.

The aims of designing a treatment technique for an individual department should be as follows: performing TBI within the department's regular schedule, using the best possible technique requiring a short treatment time, providing a comfortable positioning to patients, improving and simplifying the lung shielding system to provide reproducible positioning of the patients. Therefore, the ideal treatment technique comprises the requirements of dose homogeneity, lung sparing and dose prescription, accuracy of treatment, reproducibility and reliability of treatment set-up, comfort for

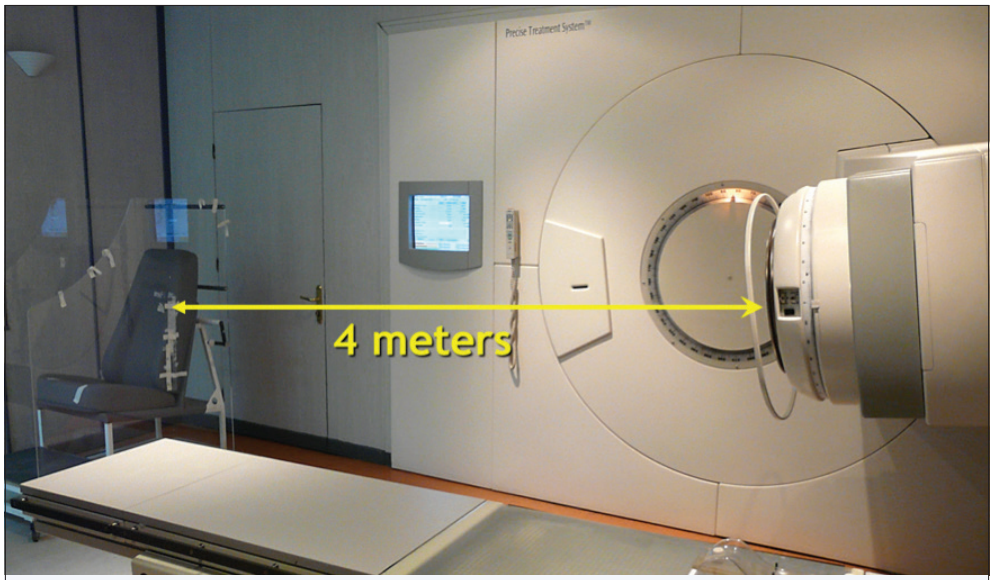

Fig. 1. TBI set-up at the Ege University Hospital. Bilateral irradiation is used with an SSD of 4 meters. Patient is seated on a specially designed chair. Plexiglas beam screens are used to increase the surface dose. Reference dose is measured by 0.6 cc ion chamber taped on the plexiglas screen.

patient and staff. The technique of TBI has evolved in parallel with an increase in the knowledge of the biologic response to ionizing radiation and improvements in radiation dosimetry and treatment delivery. Recently, new advanced techniques using helical tomotherapy and VMAT (volumetric modulated arc therapy) were implemented for TBI.[9] VMAT dose distribution was better than conformal techniques but total treatment time was unacceptably longer (coach time was 2 hours per day) for daily use especially for small kids. Longer treatment times was also reported with helical tomotherapy.[7] Another disadvantage of helical tomotherapy is the limited treatment length of the longitudinal axis, allowing a maximum PTV length of 145 cm. Patients exceeding 145 cm body length require another complex plan for lower part of the body, which extends the total treatment time further.

The best total radiotherapy dose and dose rate are other unanswered questions in clinical practice. Several authors tried to find a relationship between the total dose of TBI and treatment outcome. Although some of them reported a higher overall survival with increasing TBI dose,[10] others reported opposite.[11] Vriesendorp et al.[12] reported that the results of TBI is related with dose, fraction size and endpoint selection and that different TBI procedures could not be compared without radiobiological "normalization". This normalization will also be different for various endpoints. Relapse rates were significantly lower in the TBI schedules using higher doses but disease-free survival and treatment-related mortality were significantly different in various trials.[13]

Acute and especially long term side effects are the major concern for TBI protocols.[14] Most centres use fractionated TBI to reduce acute side effects such as nausea and vomiting, and late effects such as cataracts. Shielding of the lungs to keep the total lung doses under 10 Gy is also widely used to prevent severe radiation pneumonitis. In Europe, most centres do not irradiate children below the age of 2 years due to the harmful effects on the developing brain. The biggest risks for children who received TBI are the secondary malignancies, growth retardation (especially if irradiated below 10 years) and infertility (most common after irradiation during or after puberty).

To date, it has not been shown that TBI in the conditioning regimen for childhood ALL can be replaced by chemotherapy. Davies et al. compared outcomes of HLA-identical sibling transplants for ALL in children who received cyclophosphamide CY/TBI (n=451) versus those who received Bu/CY (n=176) for pre-transplant conditioning. The 3-year probabilities of survival were 55% with TBI/CY and 40% (95% CI 32% to 48%) with Bu/CY (univariate p=.003). In a multivariate analysis, the risks of relapse were similar in the two groups (relative risk [RR], 1.30 for Bu/CY v CY/TBI; p=.1).

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Treatment related mortality was higher in the Bu/CY group (RR, 1.68; p=.012). Death and treatment failure (relapse or death, inverse of leukaemia-free survival (LFS)) were more frequent in the Bu/CY group (RR, 1. 39; p=.017 for death; RR, 1.42; p=.006 for treatment failure).[4] Bunin et al. performed a randomized trial of oral Bu vs. TBI in children with ALL. There was no significant difference between Bu and TBI for patients who received stem cells from related donors (36% vs 58%). However, for unrelated donors, EFS was 20% for Bu and 57% for TBI. Relapse was similar in both arms. [5] The available reports did not clarify whether all allogenic stem cell transplant patients need a TBI containing regimen.[14,15]

In conclusion, TBI has been used most frequently for allogenic transplantation in patients with acute leukaemia before HSCT. The main drawbacks of allogenic transplantation are early transplant-related mortality and late complications with the latter impacting both quality of life and patient outcomes. At present, there are a lot of unanswered questions about TBI techniques, indications and dose. Developing national protocols will improve TBI procedures in our country.

Disclosure Statement

The authors declare no conflicts of interest.

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