The Efficiency and Toxicity of Hemithoracic Radiotherapy After Extra Pleural Pneumonectomy in Malign Pleural Mesothelioma

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ABSTRACT

In this study, we evaluated the efficiency and the toxicity of three dimensional conformal hemithoracic radiotherapy (3DCHRT) after extra pleural pneumonectomy (EPP). The median age of 14 patients were 51 years (range, 33-61 years). Most commonly seen histopathology was epitheliod type (79%). According to American Joint Commission on Cancer (AJCC) 2002 staging system 9 cases (64%) were stage III. A total median dose of 50.4 Gy was applied to hemithoracic cavity. Eleven patients received adjuvant chemotherapy. 3DCHRT was generally well tolerated. The acute toxicities of 3DCHRT were grade I-II. After a median of 16 months follow-up, intrathoracic control was100%. Six patients (43%) developed abdominal relapse and one (7%) developed distant metastasis. Nine cases were dead with two of them being without the evidence of disease. Excellent local control with 3DCHRT after EPP seems to change the relapse patterns of MPM. More effective systemic treatment is needed to prevent the recurrences outside thorax.

Keywords: Malign pleural mesothelioma, Extra pleural pleurectomy, Three dimensional conformal radiotherapy

ÖZET

Malign Plevral Mezotelyomalı Olgularda Ekstra Plevral Pnömonektomi Sonrası Hemitorasik Radyoterapinin Etkinliği ve Toksisitesi

Bu çalışma kapsamında EPP sonrası üç boyutlu konformal eksternal radyoterapinin (3BKRT) etkinlik ve toksisitesinin değerlendirilmesi hedeflenmiştir. En sık görülen histopatoloji epitelyal tipti (%79). American Joint Commission on Cancer (AJCC) 2002 evreleme sistemine göre bir olgu (%7) evre I, 4 olgu (%29) evre II, 9 olgu (%64) evre III olarak kabul edildi. Hemitoraksa 1.8 Gy/ gün fraksiyon dozu ile toplam medyan 50.4 Gy 3BKRT uygulandı. Onbir hasta platin ve pemetreksed kombinasyonundan oluşan adjuvan kemoterapi aldı. Radyoterapi (XRT) sırasında gözlemlenen akut toksisiteler grad I-II olup tedavi iyi tolere edilmiştir. Medyan 16 aylık izlem sonucu lokal kontrol %100'dü. Hastaların 6'sında (%43) abdominal relaps, birinde (%7) uzak metastaz gelişti. İkisi hastalık dışı nedenlerle olmak üzere 9 olgu (%64) kaybedildi. 3BKRT ile lokal kontrolün sağlanması relaps şeklini değiştirmiş görünmektedir. Toraks dışı relapsların önlenememesi daha etkin sistemik tedavi gerekliliğini düşündürmektedir.

Anahtar Kelimeler: Malign plevral mezotelyoma, Ekstra plevral pnömonektomi, Üç boyutlu konformal radyoterapi

INTRODUCTION

Malign pleural mesothelioma (MPM) is a rare neoplasm with an estimated annual incidence in the United States of 2000 to 3000 cases. Turkey has one of the highest incidences of disease because of the geology of the country that includes several outcrop of asbestos and its widespread use by rural population.[1] The estimated incidence of mesothelioma has been reported to be 996/100.000 in the Cappadocian region of Central Anatolia where highly carcinogenic erionite fibers have been found.[1]

MPM was historically considered to be rapidly fatal. In its natural course median survival ranges from 4 to 13 months.[2] Death is frequently due to the local progression of the disease resulting in respiratory failure, pneumonia, myocardial dysfunction and dysphagia.[2]

Radiotherapy (XRT) is not used as a primary form of treatment but it is effective in prevention of chest wall recurrences after thoracotomy and thoracoscopy and palliation of dyspnea, pain and superior vena cava syndrome. Chemotherapy (ChT) helps symptom palliation and improves the quality of life. Multiagent ChT shows improvement in response rates compared to single agent regimens. Currently antimetabolite and platinum combinations which showed improvement in survival are recommended for MPM treatment.[3,4]

Surgery improves local control but it is inadequate solely. Two operation types made for curative purpose are extra pleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). EPP is an aggressive surgical procedure where the ipsilateral lung, parietal and visceral pleura, pericardium and hemidiaphragm are resected en bloc. Owing to the removal of the entire ipsilateral lung it is possible to apply high XRT doses without toxicity and improve local control.[5]

Studies assessing the efficiency of single–modality treatment, surgery, ChT or XRT have not revealed a clear benefit.[6] The recommended treatment strategy for eligible patients is adjuvant hemithoracic XRT following EPP.[5,15] Trimodality approaches including ChT also seems to end up with promising results.[7,8]

In this study we evaluated the efficiency and the toxicity of three dimensional conformal hemithoracic radiotherapy (3D CHRT) after EPP.

PATIENTS AND METHODS

Patients referred to our clinic after EPP were evaluated. Patients were eligible for the study if they have a disease localized to single hemithorax. Other requirements included age less than 70, Karnofsky performance status ≥ 70, normal renal, liver, pulmonary and cardiac function tests, normal echocardiography and electrocardiography findings. All patients had thoraco abdominal computed tomography (CT) prior to surgery, some patients 6 had preoperative positron emission tomography-CT (PET-CT) as well. Thoracic magnetic resonance imaging was performed prior to surgery to evaluate the disease relationship with diaphragm. Patients were considered ineligible if they had a previous history of XRT to thorax or abdomen, breast-feeding or pregnant. The study was approved by the Hacettepe University Faculty of Medicine Ethics Board (LUT 07/38-27) and informed consent was obtained from patients entered into the study.

Surgery

During EPP operation ipsilateral lung was removed together with parietal pleura, visceral pleura, pericardium and hemidiaphragm. Then the hemidiaphragm and pericardium were reconstructed to prevent the herniation of the abdominal organs to the chest. The ipsilateral mediastinal lymph nodes (LN) and the port sites of the previous thoracoscopy and drain sites were resected. Three centers referred their patients to XRT were in close corporation.

Radiotherapy

Adjuvant XRT started 4-6 weeks postoperatively. Treatment was planned and delivered in three dimensional conformal technique. Clinical target volume (CTV) encompassed the entire ipsilateral hemithorax from the thoracic inlet to the diaphragm insertion covering the mediastinal pleura and pericardial bed medially and thoracic wall (including the thoracotomy and chest tube insicions) laterally (Figure1). Bolus was routinely placed over the scar sites.

Treatment plan consisted of multiple phases when the dose to the spinal cord, liver, kidney, heart and stomach were found to be over tolerance limits. Customized cerrobend blocks were used to limit the dose and electrons were used to prevent underdosing in blocked regions. The dose was normalized

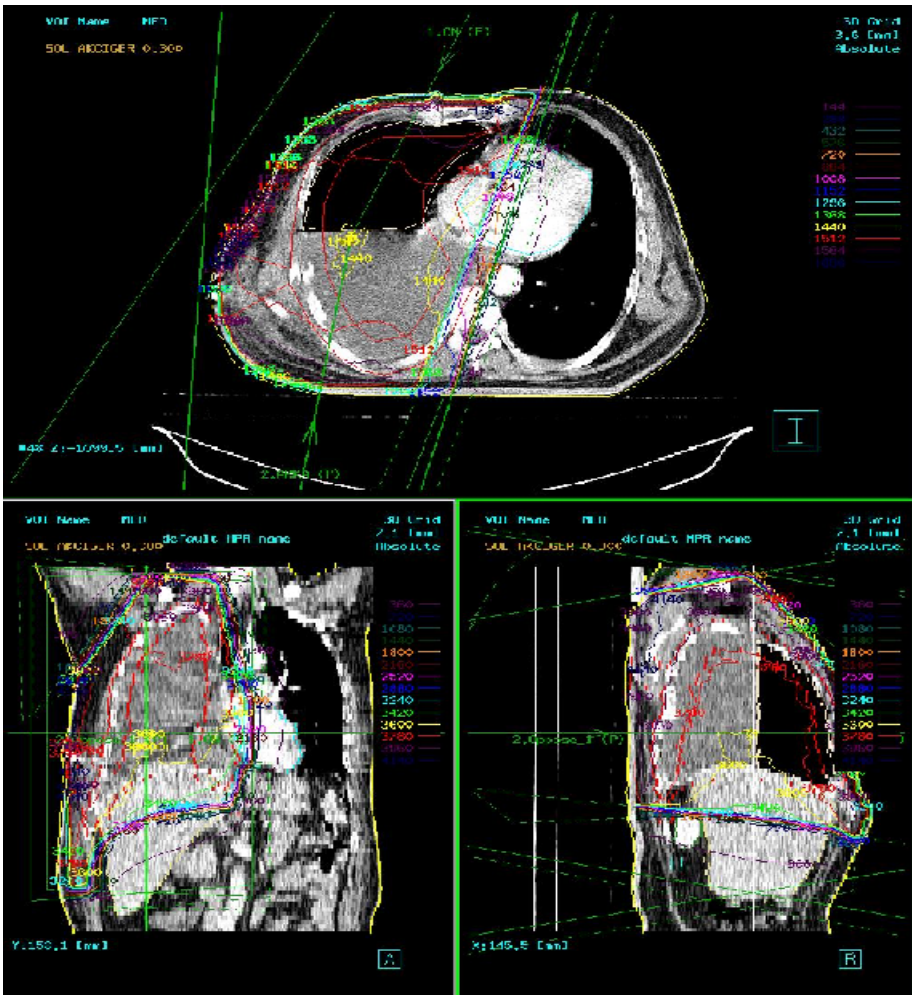

Figure 1. Transverse, coronal and saggital sections of 3D hemithoracic radiotherapy planning

to the 90% isodose line. A total 50.4 Gy was delivered in 28 daily fractions of 1.8 Gy by using 6MV photons and appropriate electron energy combinations.

Post-treatment Follow-up

Physical examination, complete blood counts, liver, renal, cardiac function tests, echocardiography, electrocardiography and imaging studies (thoracoabdominal CT or PET-CT) were performed every 3 to 4 months after the end of 3DCHRT for the first year and every 6 months thereafter.

Toxicity were evaluated on-treatment and follow-up visits and graded according to "RTOG acute radiation morbidity scoring criteria" and "RTOG / EORTC late radiation morbidity scoring schema". All patients were followed up until death or the final date of analysis.

Statistics

Descriptive statistics were used to define the study group. Survival and local control data from the date of diagnosis to the event date were plotted with the Kaplan-Meier method. SPSS 13 (SPSS Inc, Chicago, IL) was used for all statistical analysis.

RESULTS

Patient Characteristics

In this study between September 2004 and June 2007, 14 patients (4 female, 10 male) referred to our department for 3D CHRT after EPP were assessed. The median age was 51 years (range, 33-61 years), and 12 patients (86%) had white stucco history. The disease was left sided in 8 cases (57%) and right sided in 6 cases (43%). Median 18 LN's (3-40 LN) were resected. Most commonly seen his-

Table 1. The characteristics of patients receiving XRT

Patient characteristics	Number	%
Gender		
Male	10	71
Female	4	29
Histology		
Epithelioid	11	79
Biphasic	3	21
Tumor Stage (AJCC 2002)		
T1	1	7
T2	5	36
T3	8	57
LN Stage (AJCC 2002)		
N0	11	79
N2	3	21
Stage Group (AJCC 2002)		
I	1	7
II	4	29
III	9	64

topathology was epithelioid type (79%). According to AJCC 2002 staging system 1 case (7%) was stage I, 4 cases (29%) were stage II, 9 cases (64%) were stage III. Data related to the patient characteristics are shown in Table 1.

Radiotherapy

XRT duration was median 42 days (24-55 days). The patients received a median dose of 50.4 Gy of radiation (34.2-60.4 Gy). The treatment was stopped in one patient at 34.2 Gy due to emphyema developed secondary to surgery. One patient with positive surgical margins received a boost dose of 10 Gy to involved areas with the guidance of preoperative PET-CT and postoperative pathology report.

Chemotherapy

Eleven patients (79%) received median 4 cycles (range, 2-4 cycles) of adjuvant ChT after XRT. All patients except one received cisplatin (75mg/m^2) and pemetrexed (500 mg/m^2) combination every 21 days. Only one patient received carboplatin rather than cisplatin.

Relapses and Survival

With a median follow-up of 16 months (range, 5-39 months), intrathoracic control rate was 100%. Six (43%) patients developed abdominal relapse and one (7%) patient developed distant metastasis. Median time to abdominal relapse was 13 months (range, 10-17 months). Five of the patients with abdominal disease received adjuvant ChT previously. Nine cases (64%) were dead with two of them being without the evidence of disease. The relapse patterns and the treatment characteristics are shown in Table 2.

The median survival was 17.4 months (95% confidence interval, 11-24 months). 1 and 2 year overall survival rates were 76% and 25%. The median disease free survival was 15.3 months (95% confidence interval, 12-19 months). 1 and 2 year disease free survival rates were 73% and 31%. In this study, the number of the patients was small to make a reliable estimation of the prognosis. Therefore prognostic factor analysis was not performed.

Table 2. The treatment characteristics and the relapse patterns of patients

Case No	Sex	Age	Stage	XRT Dose (Gy)	ChT	Relapse	Time to Relapse (month)
1	M	55	III	50.4	+	Abdomen	13
2	F	54	III	50.4	+	Abdomen	11
3	M	39	III	50.4	+	Abdomen	17
4	M	46	II	50.4	-	Abdomen	10
5	M	61	II	50.4	+	Abdomen	15
6	M	51	III	50.4	+	Abdomen	13
7	F	41	III	60.4	+	Bone mts	8

Toxicities

Acute toxicities

In general, XRT was well tolerated with most toxicities of being grade I and II. They are commonly related to skin and upper gastrointestinal system (Table 3). Grade III hematologic toxicity was observed in one patient (hemoglobulin= 6.5) and he completed the treatment after blood transfusion without complications.

Late toxicities

Most commonly seen late toxicity was grade I radiation dermatitis that was observed in 9 patients (64%). Four patients with grade III cardiac toxicity were observed. They were reported to have pericardial effusion on their control thoracic CT and echocardiography in the 8, 9 and 10th month follow-up visits. Only one patient was symptomatic and after the drainage of the effusion he is still alive 30 months after XRT with no evidence of disease.

On his 3rd month follow-up visit one patient with right-sided disease had thoracoabdominal CT and PET-CT findings of a band-like area in the periphery of the liver under diaphragm suspicious of metastasis. PET-CT was performed and it revealed increased flouro 2-deoxy d-glucose (FDG) uptake in the neo-diaphragm adjacent to liver. Considering the diaphragmatic graft used for repair and the linear shape of the uptake it was decided that foreign body reaction secondary to diaphragmatic graft was responsible for increased FDG uptake. On follow-up CT scans there was no sign of local recurrence and the patient is alive with no evidence of disease 30 months after XRT.

DISCUSSION

MPM is an uncommon neoplasm with a historically poor prognosis. Without treatment patients die within few months after the diagnosis.[2] No single treatment modality is effective in curative intent. However recent studies showed improvements in local control and survival with multimodal approaches.[5,7-11]

In a study by Rush et al. 54 patients with MPM underwent EPP followed by 54 Gy hemithoracic XRT. The median survival was 17 months and the overall survival rate at 3 years was 27%. The sites of recurrence were locoregional in 2, locoregional and distant in 5, and distant only in 30.[5] In our study median survival was 17 months, 1 and 2 year overall survival rates were 76% and 25%. Disease free survival rates at 1 and 2 years were 73% and 31%. Although our total XRT dose is less than the dose delivered by Rush et al. no intrathoracic recurrences were observed. Both studies have the same median survival duration of 17 months.

In our study 11 patients received adjuvant ChT after XRT. There are few studies in literature about three modal treatment approaches. Baldini et al. reported their results in 49 patients who underwent EPP. Thirty-five of the surviving patients received adjuvant ChT followed by XRT. Ten patients received adjuvant ChT without XRT. Median 4 cycles of ChT including cyclophosphamide, doxorubicin, and cisplatin combination (CAP) was delivered. The prescribed dose was 30.6 Gy to hemithorax followed by a boost to bring the dose to 50 Gy in high risk areas. Recurrence rate was 54% with a median time to first failure of 19 months. The sites of first recurrence were local in 35% of patients, abdominal in 26%, the contralateral thorax in 17%, and other distant sites in 8%. Median time to relapse was longer in the patient group who received XRT (20 versus 11 months). In the multimodal treatment group median survival was longer of being 22 months.[7] Sugarbaker et al. performed EPP to 183 patients followed by CAP or carboplatin and paclitaxel ChT and subsequent hemithoracic XRT at a median dose of 30.6 Gy. Patients received concomitant paclitaxel with XRT. Boost dose was given in case of presence of residual disease, positive surgical margins and localized LNs to bring the dose to 54 Gy. The overall median survival was 19 months, the 2 and 5 year survival rates were 38% and 15%. In a subgroup of patients with epithelioid histology, negative surgical margins and negative LNs median survival was 51 months, the 2 and 5 year survival rates were 68% and 46%.[8]

In both studies mentioned above hemithoracic XRT doses were less than our treatment dose and XRT was started after ChT. The high rate of local relapses may be due to these factors. Baldini et al. showed 26% abdominal relapse and 8% distant metastasis rates.[7] High dose hemithoracic XRT improves local control and more patients apply with abdominal relapse. In our study 11 patients received cisp-

Table 3. Acute toxicities of XRT

Toxicity	Grade I	Grade II	Grade III	Grade IV	Grade V
Dermatitis	10	-	-	-	-
Dysphagia	4	1	-	-	-
Nausea-vomiting	2	8	-	-	-
Cough	4	1	-	-	-
Anemia	1	-	1	-	-
Neutropenia	1	-	-	-	-

latin-pemetrexed combination ChT that has a known survival advantage.[3] XRT was delivered in 3D conformal technique and started within 53 days after surgery. In the literature there is no study with the same treatment order (EPP-XRT- ChT), hemithoracic XRT dose and ChT regimen. Our intrathoracic control rate was 100% while 7 relapses were observed (6 abdominal and 1 distant).

Abdominal relapses in patients with MPM may be due to the direct extension, presence of residual disease, tumor implantation during surgery or existence of multifocal disease. Detailed preoperative evaluation of the patient is essential. PET-CT may be effective in showing the active disease sites, transdiaphragmatic extension of the disease and distant metastasis.[12,13] Although EPP is a highly aggressive surgery within expert hands morbidity and mortality rates are quite low. It is the most important component of curative treatment and extra caution must be given to not to destroy the peritoneum while removing the diaphragm during surgery. Hemithoracic XRT treatment port should include surgical clips, diaphragm and pericardium.

In our study 5 among 6 patients with abdominal relapse received adjuvant ChT after 3DCHRT. The presence of relapse after systemic treatment may be because of the inadequacy of current diagnostic work-up and systemic treatment. Rice et al. evaluated 118 patients with radiological and clinically resectable MPM using laparoscopy-peritoneal cytology and mediastinoscopy. 11% patients had abdominal disease and 4% had contralateral LN positivity. As a result 13% of patients showed advanced disease and EPP was abandoned.[14] Laparoscopy-peritoneal cytology and PET-CT should be used in the preoperative evaluation of the patients. It is also crucial to not to destroy the peritoneum during surgery to prevent local relapse.

Most of our patients were with stage III disease. Neoadjuvant treatment strategies showed encouraging results in stage III and IV disease. Flores et al. operated 9 stage III-IV patients after 4 cycles of gemcitabin and cisplatin combination ChT and 8 of them received 54 Gy hemithoracic XRT. Median survival was 33.5 months in the surgery group while 9 months in the non-surgery group.[9] In a pilot study Weder et al. treated T1-3, N0, M0 patients with 3 cycles of neoadjuvant gemcitabin and cisplatin combination ChT. Six-teen patients were operated and 13 of them received XRT. XRT doses were 30 Gy to hemithorax and 20-30 Gy boost to high risk areas. Median survival was 23 months.[10]

In a multicenter phase II Swiss Study same ChT regimen was delivered to 61 patients in all stage groups. After EPP 36/61 patients received XRT. XRT portal includes the incomplete resection sites and the high risk areas defined by the surgeon. Median survival was 23 months in the EPP group. Postoperative morbidity and mortality rates were 35% and 2.2%.[11] Although these studies have some similarities, XRT protocols and disease stages were different. The results of additional studies of multimodality treatment especially with cisplatin- pemetrexed combination that includes all stages, uses PET-BT in diagnostic work-up, high dose hemithoracic XRT and cisplatin- pemetrexed combinations are anticipated.

Hemithoracic XRT was quite well tolerated in the literature. Major toxicities were grade I-II and related to upper GIS, lung, esophagus.[5,16] Our study was

consistent with these findings but 4 patients developed pericardial effusion that was accepted as grade III late cardiac toxicity. It is misleading to connect this with XRT directly because EPP is a highly aggressive surgery during which a significant part of the pericardium is resected. These factors must be considered in the evaluation of a true late radiation related toxicity as the cardiac doses received during hemithoracic XRT were below the tolerance limits in our patients.

This combined modality approach is feasible for MPM and excellent local control achieved seems to change the relapse patterns of MPM. More effective systemic treatment and preoperative work-up is needed to prevent the recurrences outside the thorax.

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