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Radiotherapy applications of patients with malignant mesothelioma: A single center experience

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ABSTRACT

Background: In the management of malignant pleural mesothelioma, radiotherapy has been used for the purpose of prophylaxis to reduce the incidence of recurrence at surgical insertion sites or palliate the symptoms.
Aim: The purpose of the study was to evaluate the techniques and effectiveness of radiotherapy in malignant pleural mesothelioma.
Materials and methods: Forty-four (18 female, 26 male) patients diagnosed with malignant pleural mesothelioma were retrospectively evaluated. All patients had surgery or thoracoscopic biopsy for diagnosis, staging or treatment and all received palliative or prophylactic radiotherapy. Fifty-seven percent of the patients received chemotherapy.
Results: Prophylactic radiation was applied to 27 patients with 4–15 MeV electron energies. The median radiotherapy dose was 30 Gy with 3 Gy daily fraction dose. During treatment, 12 patients had grade 1 erythema according to the RTOG scale. In 3 (12%) patients, a local failure at treatment field was observed. Palliative radiotherapy was applied to 17 patients for pain palliation. The median radiation dose was 40 Gy with 2 Gy daily fraction dose by using 6–18 MV photon and/or 4–12 MeV electron energies. Two patients had grade 1 erythema and one patient had grade 2 odynophagy according to the RTOG scale. For 10 (59%) patients, palliation of chest pain was delivered. No late toxicity was observed for all cases.
Conclusion: Our experience showed that prophylactic and palliative radiotherapy are effective and safe therapy modalities in malignant pleural mesothelioma in preventing seeding metastasis at intervention sites or relieving pain. Prospective randomized studies are still needed to determine the benefits of radiotherapy application and to indicate optimum dose schemes.

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1. Background

Malignant pleural mesothelioma (MPM) is a relatively rare thoracic tumor which is originates from the lining cells of the pleura.[1] The incidence of MPM is expected to increase over the next decade in most industrial countries and in the countries with poor regulations of asbestos mining, production and household use.[2,3] The domestic usage of soil mixed with asbestos causes a major health problem in Turkey, especially in Eastern and South Eastern Anatolia. A mineral other than asbestos named fibrous zeolyte (erionite) is accepted to be one of the most powerful carcinogens and was found in some rocks used in the construction of houses and in the walls of caves used as storerooms in the villages of the Cappadocia region in Turkey.[4] Asbestos and erionite are known factors in the etiology of MPM. Although it varies between series, there is a contact with asbestos in 70–80% of cases.[5–7]

MPM is considered as an aggressive disease with dismal prognosis. Median survival varies between 9 and 17 months.[8,9] Local disease progression is the main cause of death.[10,11] The major problem is poor control of local disease and the dissemination of MPM through the drain sites and tracks of chest wall instrumentation.[10] There is no definite standard of care, only a minority of patients are eligible for curative therapy. Single modality treatment [surgery, radiotherapy (RT) or chemotherapy] have generally failed to significantly improve survival.[12] Multimodality aggressive therapy seems to improve local control and survival, but the benefits of this approach have been questioned because of treatment related morbidity and mortality.[12,13] Although radical surgery has been advocated, most cases cannot be operated due to surgical or medical inoperability.[14] Many single and combined chemotherapeutic agents have been tried and reviews describe modest success with several agents.[15,16] As RT has never been compared to chemotherapy or surgery or best supportive care in prospective randomized trials, there exist no data to support one or the other therapies as a better option.[17]

MPM is tradionally thoght to be radioresistant, however, tumor cells derived from MPM were found to be more sensitive to radiation than non-small cell lung carcinoma.[18] In the management of MPM, RT is used in three ways: as prophylaxis to reduce the incidence of recurrence at sites of diagnosis or therapeutic instrument insertion, or in a multimodal treatment to improve locoregional control after resection of early-stage disease and to palliate symptoms for patients with advanced disease.[7] Mesothelial tumor cells seeding through the instrument tracts after pleural intervention occurs in around 20%, but may be as high as 50%.[19–21] In the presence of seeding metastasis, the lesion can be extremely painful and difficult to palliate with RT,[21] and surgery is the only effective procedure if applicable.[10] For this reason, prophylactic RT to drain sites or incision scars is the main preventing option.[7,21] However, no clear consensus on the benefit of prophylactic RT can be reached, because the trials have conflicting results.[7,12] Moreover, RT has been applied to relieve symptoms associated with MPM. Althogh previous studies had confimed that RT can palliate chest pain in nearly 60% of patients,[22–24] no optimal RT dose and fractionation scheme has been specified from these studies.

2. Aim

Rarity of this disease and few available retrospective and prospective data led us to review our experience. The purpose of this study was to evaluate the tecniques and effectiveness of RT when given on a prophylactic and palliative basis either alone or combined with chemotherapy in MPM patients.

3. Materials and methods

We retrospectively evaluated the files of cases with MPM, treated at Gazi University Faculty of Medicine, Department of Radiation Oncology between 1996 and 2010. The informed consent form was obtained from all patients. Forty-four patients (18 female, 26 male) with a median age of 55 (range 36–84) years at diagnosis were assessed. Dyspnea (87%), chest pain (75%) and cough (65%) were the most common presenting symptoms. All patients' Karnofsky Performance Statuses were $\geq$70. These patients underwent detailed investigations before therapy. Routine blood tests, chest X-ray, chest and abdomen computed tomography, pulmonary function testing, and, more recently, positron emission tomography were performed. The MPM diagnoses were histopathologically proven for all cases. Epitheloid subtype was reported in 38 (86.4%) patients while biphasic subtype in 6 (13.6%) patients. Video-assisted thorascopic surgery (VATS) and pleural biopsy were applied to 9 (20.5%) patients, 9 (20.5%) patients had pleural decortications, 2 (4.5%) patients had thoracotomy and wedge resection, 2 (4.5%) patients had thoracotomy and pleurodesis, 5 (11.4%) patients had biopsy and pleurodesis and 17 (38.6%) patients had only biopsy. Twenty-five (57%) patients received chemotherapy and different drug regimens were used. Most patients received gemcitabin and cisplatin or cisplatin and pemetrexed and remaining patients received different protocols including ifosfamide, epirubicin and adriamicin. Chemotherapy was usually applied in 4–6 cycles. All patients received RT. Six weeks after completion of RT and within 3 months' interval thereafter, patients were followed-up with physical examination, routine blood chemistry, chest X-ray and/or computed tomography. If any suspicious lesions were observed, biopsies were taken for histopathological confirmation. For the evaluation of pain response, patients were revised at 1 month after completion of RT. Evaluation of pain relief (patient reported) or other symptomatic response was based on patient records. Pain was evaluated by using a visual analog scale.

The statistical analysis was performed by using the Statistical Package for Social Sciences software package, version 13 (SPSS Inc., Chicago, IL, USA). Patients and treatment characteristics were described using median, mean, standard deviation and range (minimum–maximum) for continuous variables. The follow-up time was estimated from initial date of RT to date of death or last follow-up. The survival time was estimated from date of the histopathologic diagnosis to date of death or last follow-up. The survival analysis was performed by using the Kaplan–Meier method.

Table 1 – Prophylactic radiotherapy features and treatment responses.

[a]RT planning ($n = 27$)	
[b]2DCRT: 13 (48.2%)	
[c]3DCRT: 14 (51.8%)	
[a]RT dose-fractionation schedules	
Total [a]RT dose: median 36 (range: 21–42) Gy	
Daily [a]RT dose: median 3 Gy (range: 2–7) Gy	
Fraction numbers: median 12 (range: 3–21)	
Treatment response	
Local and distant failure	Patients (n, %)
[a]RT field	3 (12)
Ipsilateral hemithorax	7 (28)
Ipsilateral hemithhorax + mediastinum	4 (16)
Contralateral	2 (8)
Distant metastasis	6 (24)
Survival	
Mean survival time: 12.6 ± 1.3 (10–15) months	
1 year survival rate: 61%	
2 year survival rate: 4%	

[a] RT, radiotherapy.
[b] 2DCRT, two dimensional conventional radiotherapy.
[c] 3DCRT, three dimensional conformal radiotherapy.

4. Results

Twenty-seven (61.4%) patients received RT for prophylaxis, 17 (38.6%) patients received RT for palliation. Twenty-three (52.3%) patients received conventional RT and 21 (47.7%) patients received three dimensional conformal RT (3DCRT). Conventional two dimensional RT (2DCRT) was applied to 13 (48.2%) and three dimensional conformal RT (3DCRT) was applied to 14 (51.8%) 27 patients in the prophylactic intent (Table 1). Palliative 2DCRT was performed for 10 (58.8%) patients while 7 (41.2%) patients received 3DCRT (Table 2).

For conformal RT, computed tomography planning scans were used. On each tomography slice clinical target volume (CTV), planning target volume (PTV) and organ at risk (OAR) were contoured. For prophylactic 3DCRT, all procedure scar sites (fine needle biopsy, drainage, thoracoscopy, thoracotomy, pleurectomy); for palliative 3DCRT, all sites of symptomatic and bulky disease were included in CTV.

Prophylactic RT was applied after healing of the surgical scars, 8–69 (mean 35) days after procedure. For prophylactic radiation, 1–1.5 cm margin was added to incision or dren scars. The appropriate electron energies such as 4–15 MeV were used for 35 drain sites (minimum one maximum three sites for each patient). The median RT dose was 30 Gy with 3 Gy daily doses. In some cases, bolus material was used. The RT was well tolerated. During RT, 12 (44.4%) patients developed grade 1 erythema [Radiation Therapy Oncology Group (RTOG) scale]. RTOG ≥grade 2 acute skin toxicity was not observed. No late complications (such as skin fibrosis, necrosis or lung toxicity) were observed. The response of prophylactic radiotherapy was evaluated for 25 patients, because two patients were lost to follow-up. In 3 (12%) patients, local failure at the radiation treatment fields was observed. Local and distant recurrences were seen in 17 of 25 patients. The most metastatic site was the bone. Twenty-two of 25 patients died after a mean follow-up time of 10.5 (1.3–28) months. The mean survival time was 12.6 months. Prophylactic RT dose-fractionation schedules with treatment response are summarized in Table 1.

Palliative RT was applied to 17 patients with local-advanced stage MPM for pain palliation. The median RT dose was 40 Gy with 2 Gy daily fractions by using 6–18 MV photon and/or 4–12 MeV electron energies. For one patient, Co60 device was used. For one field the total dose remained at 26 Gy due to patient's own request for leaving the therapy. Therefore, he was excluded from the analysis of treatment response. The median duration of pain relief was found to be 3 (2–6) months. RT was well tolerated. During RT, 2 (11.8%) patients had grade 1 erythema and 1 patient (5%) developed grade 2 odynophagy according to RTOG scale. No radiation induced pneumonia and no late complications (such as skin or lung fibrosis) were observed. For 10 (59%) patients, chest pain relief was reported. In 10 patients local failure, in 3 patients distant metastasis and in 3 patients local failure and distant metastasis were observed. All patients died after a mean follow-up time of 6.9 (0.6–16.5) months. The mean survival time was 11.6 months. The palliative RT dose fractionation schedules with treatment results were summarized.

Table 2 – Palliative radiotherapy features and treatment responses.

[a]RT planning ($n = 17$)	
[b]2DCRT: 10 (58.8%)	
[c]3DCRT: 7 (41.2%)	
[a]RT dose-fractionation schedules	
Total [a]RT dose: median 40 (range: 20–60) Gy	
Daily [a]RT dose: median 2 Gy (range: 2–4) Gy	
Fraction numbers: median 12 (range: 5–30)	
Treatment response	
Local and distant failure	Patients (n, %)
Progression in [a]RT field	4 (25)
Outside [a]RT field	6 (37.5)
Distant metastasis	3 (19)
Outside [a]RT field + distant metastasis	3 (19)
Survival	
Mean survival time: 11.6 ± 0.9 (10–13) months	
1 year survival rate: 53%	
2 year survival rate: none	

[a] RT, radiotherapy.
[b] 2DCRT, two dimensional conventional radiotherapy.
[c] 3DCRT, three dimensional conformal radiotherapy.

5. Discussion

Retrospective studies have reported that prophylactic RT can prevent MPM metastasis in surgical intervention sites.[25,26] However, three small prospective trials have had conflicting results. The first randomized phase III study from France[19] compared the 20 patients who had received prophylactic RT to surgical sites to 20 patients who had not received RT. Patients were treated with 21 Gy in 3 fractions by using 12–15 MeV electrons. No patients in the irradiated group had recurrence along intervention sites, whereas 40% of patients had metastatic nodules in the non-irradiated group. On the other hand, the randomized clinical trial from England[27] showed no benefit of prophylactic RT. In this study, 31 MPM patients, who had had

pleural invasive procedure, received 21 Gy in 3 fractions using 250 kV or 9–12 MeV electrons, another 30 patients received best supportive care. No statistically significant difference was found in the risk of tract metastasis between the arms. In the third trial conducted in Australia,[28] 28 patients received 10 Gy in a single fraction using 9 MeV electrons within 15 days of invasive procedure. Thirty patients did not receive radiation. The difference in tract metastasis between the groups was not significant. However, the authors indicated that 9 MeV may have been inadequately penetrating. It is difficult to deduce a conclusion from these results. Since all three trials included small numbers of patients and the radiation techniques used different dose-fractionation Schemes.[7] Based on existing data, no clear consensus can be reached as to the benefit of prophylactic radiation. However, despite the absence of large randomized controlled trials, the reported series showed that most of the clinicians preferred to apply prophylactic RT. Recently, a survey practice in the Netherlands and Belgium showed that 32 of 38 centers that responded to questionnaire recommended prophylactic radiation to intervention sites[26] and a study from the United Kingdom showed that 75% of 23 oncology centers offered to use prophylactic RT.[29]

In our department, the general approach is applying prophylactic radiation to intervention sites. Although there was no consensus on dose fractionation schedule, hypofractionated schemes were mostly preferred and applied within a mean of 35 days after procedure. In the literature, the optimum dose and timing of RT has not been clear, however, based on retrospective studies hypo-fractionated RT has frequently been a preferred regimen.[19,26,30] The National Comprehensive Cancer Network (NCCN) recommends doses of 21 Gy in 3 fractions for prophylaxis. Although in recent years 21 Gy has been preferred in our department, the most used schedule being 36 Gy in 12 fractions. The reason to use 36 Gy was that according to the isoeffective dose formula, when the α/β ratio was accepted as 1.7 due to subcutan tissue for late reactions,[31] the effectiveness of 36 in 12 fractions was equal to 46 Gy in 23 fractions, radiobiologically, which was accepted sufficient dose for prophylaxis.

In several reports, RT was applied within 2–3 weeks after surgery.[25,27,32] It is difficult to draw definitive conclusions as to the timing of prophylactic RT. Actually, best timing for delivering radiation after surgical intervention should be determined by a multidisciplinary team. In our hospital, starting prophylactic RT within 3–6 weeks after surgery has been recommended. Our results indicated that prophylactic RT was an effective and safe treatment modality for patients with MPM. One difference of this trial from several previous studies is that 3DCRT was applied to 52% of the patients. This can be one of the reasons for observing minimal side effects with high local control ratios due to obtaining more homogenous dose distribution while protecting more surrounding normal tissues compared to conventional RT technique.

Chest wall pain is one of the frequent symptoms of MPM. The studies that evaluated the effectiveness of palliative RT were usually retrospective and an optimum dose and fractionation scheme was not clear. In an early retrospective trial, 29 courses were given to 19 patients with doses of 40–50 Gy and effective palliation was associated with $\geq$40 Gy RT.[32] In another study, 21 patients undergoing a total of 31 courses of palliative RT were evaluated. Short courses of RT (20 Gy in 5 fractions) seemed to be as effective as longer courses (30 Gy in 10 fractions) of RT for relieving the symptoms.[33] Bissett et al.[22], prospectively assessed the pain response of a large field RT given to the hemithorax to a dose of 30 Gy in 10 fractions. In that study, the effectiveness on pain palliation was evaluated by using a visual analog scale and the consumption of analgesics before and after RT. Pain control was obtained in 13 of 19 (68%) patients at 1 month after RT. However, this response was short-lived; In 9 of 12 patients, chest pain worsened by 3 months. Similar results were found in another retrospective analysis. Higher local response rates for patients treated with 36 Gy applied using 4 Gy per fraction were compared to those receiving 30 Gy with less than 4 Gy per fraction (50% vs. 39%). The evaluation of response was based on patients' report and the use of analgesics. The duration of pain relief was again short and it was recurred at a median of 69 days after RT.[24] The criticism of these reports is the following; patient numbers were small, RT techniques used in most cases were obsolete, and measures of symptom control were not standardized. In our study, palliative RT was applied to 17 patients for pain palliation. Total doses were heterogeneous such as in other retrospective studies and varied from 20 Gy to 60 Gy. This variation could result from the necessity of applying RT to large fields such as one hemithorax for controlling the symptoms. Therefore, the clinicians were compelled to modify the RT dose and fractions according to the existence of poor performance status and co-morbidities of the patients and the extensive irregularly in the shape of tumors. Forty-percent of patients received 3DCRT and at most cases the total doses were reduced to prevent early and late toxicities at many critical structures such as the heart, lung and spinal cord as a consequence of large RT volume and large fraction size. Usually, a preferred RT schedule was 40 Gy delivered by 4 Gy per fraction. As it was emphasized before that the effective palliation can be obtained with this regimen. At 1 month after completion of RT, pain control was achieved in 59% of patients. However, the duration of pain relief was not mentioned and assessment of RT efficacy on pain control was based on our patients' perception, which is subjective. In a recent study, it was shown that a significant volume of disease was omitted from the target volume in 3BCRT; since it was difficult to encompass all the tumor due to dose constraints imposed by adjacent organs. The authors stated that defining parts of the tumor responsible for symptoms and defining the duration of pain control is difficult, by its nature which is highly subjective.[29]

6. Conclusions

Our experience showed that prophylactic and palliative RT are effective and safe therapy modalities for MPM patients. Major drawbacks of our study are its retrospective nature, small number of patients and heterogeneity in dose-fractionation RT schemes. The necessity of prophylactic irradiation is still controversial, however, as seeding metastasis are painful, applying prophylactic radiation can be preferred to improve patients' quality of life. Palliative RT can certainly be of some benefit in palliating chest pain, but its duration is often short.

Although at present, no validated assessment of RT effectiveness for palliation is available, palliation of symptoms and pain relief remain important in patient care. Prospective randomized studies are needed to determine the benefits of prophylactic or palliative RT application and to indicate the optimum dose schedules.

Conflict of interest

There is no financial and personal relationship with other people or organizations.

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