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Case Report

Malignant Pleural Mesothelioma: A Multi-Disciplinary Approach

Muhammad Atif Mansha\textsuperscript{1}, Nasir Ali\textsuperscript{1}, Shaukat Ali\textsuperscript{1}, Nausheen Azam\textsuperscript{2}, Agha Muhammad Hammad Khan\textsuperscript{1}

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Abstract

**Background:** Malignant pleural mesothelioma is a rare disease with poor prognosis. Surgery is used as a radical treatment modality but the risk of local relapse is very high. Therefore, radiation therapy is used in post-operative setting to improve local control. However, owing to elliptical shape, treating the entire pleura requires a large radiation field which increases toxicity. Precision radiation is mandatory to optimally irradiate the tumor area while sparing critical neighboring normal organs.

**Case Presentation:** A 43-year-old male presented with history of right sided chest pain and cough for 8 months. On further evaluation, he was diagnosed with malignant pleural mesothelioma. The disease was localized but unresectable, therefore a course of neoadjuvant chemotherapy was given. Post chemotherapy, he underwent extra pleural pneumonectomy and the tumor was grossly excised. Histopathology revealed a close resection margin with metastasis in the regional lymph nodes. The case was discussed in multidisciplinary team meeting and adjuvant radiation therapy was offered. The patient was planned with a blend of modern intensity modulated radiation therapy technique and conventional three-dimensional conformal radiation therapy technique, to keep doses of adjacent organs within tolerance limits and at the same time deliver the intended dose of radiation to the tumor site.

**Conclusion:** Malignant pleural mesothelioma is a lethal disease. Orthodox methods of radiation delivery encompass the entire involved hemi thorax and result in significant morbidity. Highly conformal radiation techniques are preferred to achieve optimal therapeutic ratio at this site. However, despite advances in radiation techniques, current treatment modalities have not significantly made an impact on survival of these patients.

**Keywords:** Mesothelioma, Intensity modulated radiation therapy, Three-dimensional conformal radiation therapy

Introduction

Malignant pleural mesothelioma (MPM) is a deceptive disease arising from the mesothelial surface of the pleura, peritoneum, pericardium or tunica vaginalis. It is a rare entity with a median survival of less than 1 year.\textsuperscript{(1)} The treatment of mesothelioma remains a therapeutic challenge but recently there have been significant improvements in its management leading to better survival.\textsuperscript{(2, 3)} We share the case of middle aged man who was managed aggressively with multiple modalities in an effort to achieve cure.

The concavity of pleura makes it difficult to deliver a radical dose of radiation at this site. Intensity modulated radiation therapy (IMRT), an advance form of three-dimensional conformal radiation therapy (3D-CRT), was employed to deliver a dose of 54 gray (Gy) to the tumor bed while maintaining normal tissue constraints. To the best of our knowledge, this is the first case of MPM from our region, where IMRT is utilized to deliver a curative dose of radiation in adjuvant setting.

Case Presentation

A forty-three years old male, known hypertensive, presented in oncology clinic with complains of right sided

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chest pain and dry cough for 8 months. It was associated with night sweats and a significant weight loss of 13 kilograms. Upon systemic inquiry, he had chronic history of gastritis and constipation. His father died of leukemia 11 years back. By profession, he is a businessman, owning a textile mill. Currently, he has been prescribed amlodipine 10 mg per day to control hypertension. On examination, he was anemic. He had reduced chest movement on the right side along with diminished breath sounds.

He brought a computed tomography (CT) scan of the chest showing a lobulated massive nodular thickening of right pleura, involving costal and mediastinal surfaces, extending and involving the fissures. The mass was completely encasing right lung with loss of volume and mild tracheal shift to right. There was no mediastinal lymphadenopathy (Figure 1). A CT guided biopsy from the pleura was taken and sent to histopathology laboratory for further analysis. The immunohistochemical stains calretinin and cytokeratin (CK) were reactive and thyroid transcription factor was negative. The final diagnosis was reported as malignant mesothelioma (Figure 2). Once the diagnosis was established, a positron emission tomography/computed tomography (PET/CT) was done for staging purpose. PET/CT did not reveal any regional or distant metabolic activity, except for the hyper metabolic right pleura (Figure 3).

The case was discussed in multidisciplinary team (MDT) meeting to outline a treatment plan. He received six cycles of chemotherapy with cisplatin and pemetrexed. Post chemo, a CT chest was done to look for response but the disease was grossly unchanged. Patient underwent right extra pleural pneumonectomy and mediastinal lymph node sampling. Histopathology was consistent with mesothelioma. All the margins were clear except the pericardial surface margin which was 0.1 cm. A total of 11 lymph nodes were recovered, out of which 2 were positive for metastasis. Post operatively, he was given radiation to the right hemi thorax. A total dose of 54 Gy in 30 fractions was given in two phases. In phase one, 45 Gy was given to the right hemi thorax with IMRT followed by 3D-CRT boost dose of 9 Gy to close pericardial surface margin (Figure 4). During the course of radiation therapy, patient...
was assessed weekly for any acute radiation related side effects. He developed grade 1 nausea as defined by common terminology criteria for adverse events (CTCAE) version 5 and was managed conservatively.

Post treatment a PET/CT was repeated after 3 months to look for any recurrent or residual disease. There was mild thickening with focal metabolic activity in the region of right pleura which was reported as post intervention inflammatory sequel. The patient is on regular follow up with physical examination and chest imaging done every 3 months. He is asymptomatic and free of any disease clinically after 1 year.

Discussion

Mesothelioma is a rare aggressive tumor arising from the lining of the pleura, pericardium and peritoneum. Exposure to asbestos is the single most important etiological factor in mesothelioma.\(^{(4)}\) The lifetime risk of developing mesothelioma in asbestos workers is as high as 10% with a latent period between asbestos exposure and development of mesothelioma is around 20–40 years.\(^{(5)}\)

Although Trans–Atlantic guidelines do exist, there is no consensus for optimal treatment of MPM. Treatment modalities include surgery, chemotherapy, radiation therapy and immunotherapy. Being a rare entity, all the cases should be discussed by a specialized and experienced MDT consisting of thoracic surgeon, radiation oncologist, medical oncologist, diagnostic radiologist, histopathologist and pulmonologist to provide best and effective recommendation for treatment, within the available resources.\(^{(6)}\) Decision for surgery plays a vital role as it decides the intent and paves way for introduction of multimodality approach to gain maximum outcomes.
with curative intent. Two types of surgeries are commonly used in the treatment of MPM namely extra pleural pneumonectomy (EPP) and pleurectomy / decortication (P/D). Cao and his colleagues did a systematic review of the published literature and found that EPP and P/D have similar outcomes in terms of overall survival. However, these two procedures are not interchangeable and individual surgical plans should be formulated on the basis of disease extent, patient’s performance status and surgeon’s skills.

Surgery alone is not curative and reported to have a local recurrence rate of around 80%. Therefore, radiation therapy (RT) is used in adjuvant setting to improve local control. Contemporary literature endorses radiation doses in the range of 45 to 54 Gy. Owing to the anatomical complexity of the target volume, highly conformal RT techniques are employed to spare nearby organs while delivering adequate dose of radiation to the target. Higher doses up to 60 Gy can be considered but doses to contralateral lung and other critical structures like heart, spinal cord, liver and kidneys should be kept within tolerance limits. Since conventional radiation techniques are not able to spare normal organs, resulting in significant toxicity and therefore, more advance treatment techniques such as IMRT are considered.

Matsuo et al. reported the long–term outcomes of mesothelioma patients treated with IMRT. Though there was an improved median survival, ranging from 17.5 to 27 months with use of IMRT, but at a cost of grade III acute and late toxicities. Acute side effects were observed in 89% of patients stratified as hematological (42%), pneumonitis (14%) and fatigue, nausea or vomiting (33%). Similarly a quarter of patients developed late toxicities, which included grade III liver dysfunction (20%) and grade IV persistent thrombocytopenia (4 %). Allen et al. reported fatal radiation induced pneumonitis in approximately half of the patients who received a dose of 54 Gy in 30 fractions at 1.8 Gy per fraction using IMRT after EPP. A phase II European multicenter randomized study evaluated the role of postoperative hemi thoracic radiation and concluded no survival benefit. Several limitations were associated with this trial including a small cohort who received RT due to high percentage of drop out after randomization, use of variable doses and fraction sizes, slow accrual and lack of discussion on RT details and quality assurance parameters.

Contrary to this, IMPRINT trial validated the use of IMRT and concluded it as a safe option with only 8% grade III pulmonary toxicity. But the surgical modality used in this trial was P/D. Chance et al. compared the safety and efficacy of IMRT after EPP and P/D. They observed higher incidence of grade III toxicities in P/D–IMRT arm. After a median follow up of 12 months, only 8 % patients developed pulmonary toxicities in both arms.

In the past, the use of conventional radiation planning techniques to deliver high doses was limited by dose tolerance of organs at risk in close proximity. Therefore, RT doses applied were insufficient to achieve local tumor control leading to tumor bed recurrences. In cases where high doses were prescribed, the incidence of radiation related side effects was also high. We planned our patient with 3D–CRT and were not able to limit the doses of spinal cord and liver within tolerance. IMRT enabled the application of high local dose to complex shaped target volume with sparing of sensitive organs such as spinal cord, liver and heart (Table 1). IMRT is therefore considered as a minimum requirement but being located in a resource–constrained region, we are sharing our experience where we employed a combination of IMRT for low risk region and a boost dose with 3D–CRT to high risk area without compromising treatment outcome or toxicity profile.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraint Doses</th>
<th>Doses achieved with 3D–CRT</th>
<th>Doses achieved with IMRT + 3D–CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral Lung</td>
<td>&lt;20% to receive &gt; 20 Gy</td>
<td>1.5%</td>
<td>8.46%</td>
</tr>
<tr>
<td>MLD ≤ 8.5 Gy</td>
<td></td>
<td>6.3 Gy</td>
<td>11.12 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;30% to receive &gt; 30 Gy</td>
<td>98%</td>
<td>31%</td>
</tr>
<tr>
<td>Right Kidney</td>
<td>&lt;20% to receive &gt; 15 Gy</td>
<td>67%</td>
<td>35%</td>
</tr>
<tr>
<td>Left Kidney</td>
<td>&lt;20% to receive &gt; 15 Gy</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Heart</td>
<td>&lt;50% to receive &gt; 45 Gy</td>
<td>8.5%</td>
<td>6%</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Max 45 Gy</td>
<td>49 Gy</td>
<td>44 Gy</td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt;30% to receive &gt; 55 Gy</td>
<td>10%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Table 1: Tolerance doses of normal organs at risk and doses achieved with 3D–CRT and IMRT + 3D–CRT.
Abbreviations: MLD = mean lung dose, 3D CRT = three–dimensional conformal radiation therapy, IMRT = intensity modulated radiation therapy, Gy = Gray

Conclusion

MPM is a rare and lethal disease with a poor prognosis. Management is challenging and requires a multidisciplinary approach. Although inverse planning with IMRT is the standard of care, we however, utilized forward planning with 3DCRT without compromising clinical outcome. Sophisticated upgraded technology coupled with skilled use of conventional methods can provide a cost–effective patient centered approach for radiation delivery in low and middle– income countries.
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