Radiographic chest assessment of lung injury following hemithorax irradiation for pleural mesothelioma

P. Maasilta*, L. Kivisaari**, L.R. Holsti***, L. Tammilehto*, K. Mattson*

ABSTRACT: To characterize the nature, extent and time-course of radiation-induced lung injury, and to evaluate the usefulness of serial chest radiographs in this assessment, we studied 253 chest radiographs of 46 patients with pleural mesothelioma given hemithorax irradiation according to one of four different regimens: I 20 Gy; II 55 Gy; III hyperfractionation 70 Gy; IV hyperfractionation 35 Gy followed by local hypofractionation 36 Gy. Lung injury on the chest radiograph was graded from 0 (none) to V (maximal) based on the degree of loss of aerated lung tissue. Grade I changes were present 1–2 mths after radiotherapy in regimens II–IV. Grade V injury had developed in all but 3 out of 4 patients in the 20 Gy group by 6–12 months after irradiation. The extent and time-course of radiation-induced lung injury could be defined by serial chest radiographs alone. However, the documentation of tumour status and/or infections needed additional imaging or laboratory investigation, especially when grade IV–V lung injury was present. For research protocols evaluating radiation-induced lung injury serial chest X-rays are recommended at the following time-points: before treatment and 2, 6 and 12 mths after treatment, with additional computerized tomographic (CT) scans as required for differential diagnosis.

The lung is a dose-limiting organ when the thorax is irradiated [1]. The extent of radiation-induced lung injury depends on the volume of the irradiated lung, the total radiation dose delivered, the dose rate, the fractionation applied and the type of energy used [1–3]. Interactions with chemotherapy can be an additional factor [2, 4, 5]. Hemithorax irradiation of diffuse malignant pleural mesothelioma includes the whole lung of the affected side in the treatment volume and, therefore, constitutes a model for the study of human radiation-induced lung injury in large volume regimens.

In an attempt to cure or palliate patients with pleural mesothelioma, we have prospectively, during the years 1977–1988, evaluated four hemithorax irradiation protocols, all of which were part of combined modality treatment programmes [6]. Three protocols used high radiation doses. This report focuses on the usefulness of conventional chest radiographs in the study of radiation pneumonitis and fibrosis by describing the nature, extent and time-course of the radiological manifestations of lung injury following hemithorax irradiation.

Patients

All patients were treated at the Department of Radiotherapy and Oncology, Helsinki University Central Hospital. Entry criteria included histologically proven malignant pleural mesothelioma, ventilatory function adequate to allow radical radiotherapy (minimum predicted post-treatment forced expiratory volume in one second (FEV₁) >1 l·s⁻¹, (FVC) >1.5 l and diffusing capacity >30% of predicted normal), a Karnofsky index ≥ 60% and no major cardiovascular or other systemic disease.

During the years 1977–1988, 62 out of a total of 100 consecutive patients with pleural mesothelioma qualified for hemithorax irradiation. Of the 62 patients accepted, four were given erroneous dosages; three survived less than one month after radiotherapy; four had unevaluable chest X-rays, and five had undergone pneumonectomy. In the remaining 46 patients, radiation-induced lung injury could be studied on serial chest radiographs.
RADIATION-INDUCED LUNG INJURY ON CHEST X-RAY

Table 1. – Clinical characteristics of 46 patients with pleural mesothelioma

<table>
<thead>
<tr>
<th>Hemithorax radiation therapy schedules</th>
<th>20 Gy</th>
<th>55 Gy</th>
<th>70 Gy</th>
<th>35+36 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>21</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Females/males</td>
<td>4/4</td>
<td>5/16</td>
<td>2/4</td>
<td>3/8</td>
</tr>
<tr>
<td>Age, mean and (range) yrs</td>
<td>48 (24–62)</td>
<td>59 (38–75)</td>
<td>56 (43–70)</td>
<td>53 (39–71)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>epithelial</td>
<td>7</td>
<td>19</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>fibromatous</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>mixed</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stage*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>II A/B</td>
<td>6/1-</td>
<td>12/-</td>
<td>3/-</td>
<td>9/-</td>
</tr>
<tr>
<td>IIA/B</td>
<td>1/-</td>
<td>6/-</td>
<td>-</td>
<td>-/2</td>
</tr>
<tr>
<td>IV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>chemotherapy</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>6</td>
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<tr>
<td>subtotal surgical resection</td>
<td>4</td>
<td>18</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>radical resection</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>explorative thoracotomy</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Median survival from start of radiotherapy mths</td>
<td>12</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Response status after radiotherapy</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>stable disease</td>
<td>8</td>
<td>15</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>progressive disease</td>
<td>-</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*: modified from Butchart staging system [7].

The mean age of the patients was 54 yrs and 70% were male. Further patient characteristics and details of their treatments before hemithorax irradiation are given in table 1.

Treatments

Debulking surgery. The surgery consisted of subtotal (in one patient total) surgical resection of the pleural tumour, whenever possible without pneumonectomy or any other type of lung resection. If the disease was totally unresectable, tumour tissue for histological examination only was removed. In one patient, histological diagnosis was confirmed from biopsy of a subcutaneous metastasis.

Chemotherapy. After debulking surgery and prior to irradiation, 28 out of 46 patients were treated with single-agent or combination chemotherapy. Eighteen patients had contraindications for chemotherapy, or refused it, and they were treated with hemithorax irradiation immediately (>3 wks) after surgery.

Chemotherapy consisted of CYVADIC 1–6 cycles (cyclophosphamide 500 mg·m⁻² d 1, vincristine 1 mg·m⁻² d 1, 5-Fluorouracil 50 mg·m⁻² d 1) [8] (16 patients), mitoxantrone 14 mg·m⁻² 1–6 cycles given as a single agent [8] (6 patients) and of epirubicin 110 mg·m⁻² 1–6 cycles [9] (6 patients) also given as a single agent.

Radiotherapy. Radiotherapy was delayed until at least 3 wks had elapsed after chemotherapy (or thoracotomy). Hemithorax irradiation was always given from two opposed, shaped fields covering the whole pleural cavity, including the posterior diaphragmal sinus and extending at least to the XII vertebral body, the thoracic spine and the whole thoracotomy scar. The spinal cord was shielded with lead from the posterior field after 40 Gy. The liver was partly shielded from the anterior and posterior fields after 30 Gy. All treatments were given on a five day week basis.

Four different schedules of radiotherapy were used sequentially. The first schedule (20 Gy) consisted of continuous fractionation, a low total dose, 20 Gy in 10 fractions, of 2 Gy each, over 2 wks with 8 MeV photons.

The second schedule (55 Gy) was a split-course programme consisting of a 55 Gy midline dose given in 25 fractions, of 2.2 Gy each, over 7 wks with a 2 wk rest in the middle, with 8 MeV photons. The areas of macroscopic tumour received a boost of 15 Gy in six fractions, of 2.5 Gy each, over 8 days directly after the hemithorax treatment.
Fig. 1. — Scores and grades of radiologically-assessed lung injury after 20 Gy hemithorax irradiation in 8 individual patients. RT: radiotherapy.

Fig. 2. — Scores and grades of radiologically-assessed lung injury after 55 Gy hemithorax irradiation in 21 individual patients. RT: radiotherapy.
Fig. 3. - Scores and grades of radiologically-assessed lung injury after 70 Gy hemithorax irradiation in 6 individual patients. RT: radiotherapy.

Fig. 4. - Scores and grades of radiologically-assessed lung injury after 35+36 Gy hemithorax irradiation in 11 individual patients. RT: radiotherapy.
Fig. 5. - Chest X-rays of a patient given 70 Gy to the hemithorax prior to, and 1, 3, and 6 mths after treatment.
The first and second schedules were both preceded by chemotherapy with CYVADIC.

The third schedule (70 Gy) used hyperfractionation, 1.25 Gy twice daily (6 h interval), up to a total dose of 70 Gy in 56 fractions over 7 wks with a 10 day rest in the middle, with 24 MeV photons. This programme was preceded by chemotherapy with mitoxantrone.

The fourth schedule (35+36 Gy) was a combination of hyperfractionation 35 Gy in 28 fractions (1.25 Gy twice a day with a 6 h interval) over 3 wks with 24 MeV photons to the hemithorax. This was immediately followed by hyperfractionation 36 Gy in 9 fractions, of 4 Gy each, every other day over 3 wks with 24 MeV photons and/or 8–22 MeV electron treatment to local areas with macroscopic disease. This schedule was preceded by chemotherapy with epirubicin.

Radiological assessment of lung injury. All patients had a chest radiograph, posteroanterior (PA) and lateral views, (with 120 kV, at a distance of 2 m) taken before and immediately after hemithorax irradiation, and after that once a month up to 4 mths after the end of radiotherapy and thereafter at 6, 9 and 12 mths post-treatment (one of the groups had no chest radiographs taken at 1 mth and 4 mths following irradiation).

To evaluate the chest radiographs, a scoring system was established from 0 to 5. This graded radiation-induced lung injury as the degree of loss of air content of normal lung tissue: 0 = no abnormalities; 1 = slight and even decrease in air content; 2 = a few small (Ø <3 cm) patches of dense infiltration; 3 = large (Ø ≥3 cm) patches of dense infiltration; 4 = extensive dense infiltration, leaving patches of aerated normal lung only; 5 = a total lack of air-containing lung tissue.

Each injury score was multiplied by the appropriate area (as a percentage of the total area of the whole irradiated lung) and the figures added. For example, if half of the area of the lung had grade 2 changes and the other half grade 3 changes, the calculations were as follows: 50(%)x2 + 50(%)x3= 100 + 150 = 250. The scores therefore varied from 0 (all lung tissue normal) to 500 (no normal lung tissue on the irradiated side).

The numerical scores were graded as follows: 0–20 grade 0; 21–100 grade I; 101–200 grade II; 201–300 grade III; 301–400 grade IV; 401–500 grade V.

The following conditions resulted in the exclusion of a chest radiograph from this study: a large quantity of pleural fluid and/or atelectasis; heart failure; changes interpreted as due to infection or pulmonary metastasis from mesothelioma.

All radiological assessments were performed independently by an experienced radiologist without knowledge of the patients' other findings. All patients gave their informed consent and the studies were approved by the Ethical Committee of the Department of Pulmonary Medicine of the Helsinki University Central Hospital.

Results

A total of 46, 106, 44 and 57 radiographs were evaluable in the 20 Gy, 55 Gy, 70 Gy and 35+36 Gy treatment groups respectively. Figures 1, 2, 3 and 4 show the radiological scores and grades for radiation-induced lung injury in the individual patients in each treatment group.

The patients in the low-dose 20 Gy group differed from the other patients: if changes interpreted as radiation-induced lung injury appeared at all, they started 2 mths or later following the end of irradiation; after 6 mths one out of six patients had grade V injury, whereas five patients had grade 0 injury. After 12 mths, one out of four had grade V injury, but the remaining three patients still had grade 0 injury.

By contrast, in the high-dose (55 Gy, 70 Gy and 35+36 Gy) treatment groups the radiation injury seen on chest X-rays started immediately following or at 1 mth after irradiation. Six months after treatment all patients in the high-dose groups had grade II–V injury and all groups included individuals who had no normal aerated lung tissue left on the irradiated side at this time-point. Twelve months after the end of hemithorax irradiation all surviving individuals in the high-dose groups had grade IV–V radiological injury.

The first radiological changes appeared in the lower parts of the lungs and were diffuse, hazy alveolar infiltrations, which became increasingly dense and progressed to include the whole lung. There was loss of lung volume and finally shrinkage of the thoracic cage on the irradiated side. The parenchymal infiltration changed from alveolar to more interstitial, as fibrosis developed. Air bronchograms were seen in the late stages of injury. The same pattern of progression to severe grade V injury was seen in all three high-dose regimens irrespective of the restricted field size used during the second half of the fourth schedule (35+36 Gy).

A typical example of the development of lung injury on a chest radiograph is illustrated in figure 5, which shows PA chest radiographs taken prior to, and 1 mth and 6 mths after hemithorax irradiation in a patient given 70 Gy.

Tumour responses (based on CT evaluations after 1980, when CT became routinely available at our institution) and median survivals are shown in table 1. All patients died of progressive mesothelioma.

Discussion

With the increasing incidence of patients with mesothelioma [10], and the availability of new treatment techniques, it is urgently necessary to define the role of radiotherapy, and its optimal dose and fractionation schedule, in a multimodality approach. In this paper a large, prospectively evaluated group of patients was treated with one of four dose-fractionation schedules of hemithorax irradiation combined with debulking surgery and chemotherapy. The present study deals in
particular with the response of the normal lung tissue to the therapy, as assessed by serial chest radiographs.

Serial computed tomography scanning (CT) and also magnetic resonance imaging were available and have been used during the latter part of this study as part of another protocol [11]. Both of the newer imaging methods may be informative [12–14], but they are also expensive, time consuming, demanding on the patients and not always available. Therefore, we consider it important to study the usefulness of conventional chest radiographs in patient monitoring, and in the characterization of radiation-induced lung injury following hemithorax irradiation.

Our four different treatment regimens for pleural mesothelioma were developed during a period of ten years. Twenty Gy hemithorax irradiation was chosen because fractionated 20 Gy is the tolerance dose for lung tissue [15]. It proved unsatisfactory in tumour control, but produced no, or little and late-appearing radiation injury. The total dose was then increased to 55 Gy in a split-course manner [16]. This regimen again failed therapeutically and produced a large amount of normal tissue injury: the first changes were seen 1 mth after radiotherapy; after 6 mths the injury was severe in more than half of the patients, but normal aerated lung tissue could still be identified in all cases; 12 mths after treatment the injury was near total. To spare normal lung from late radiation injury the next schedule used hyperfractionation and, to improve therapy results, a higher total dose of 70 Gy. Again, the result was severe normal tissue damage and poor tumour response. The radiation injury in this group started early at completion of radiotherapy and progressed steadily until all normal lung tissue had vanished by 4–6 months after treatment. The rationale for the 35 +36 Gy schedule was to combine normal tissue sparing hyperfractionation with hypofractionation of 4 Gy every other day (we have observed that chest wall recurrences of mesothelioma respond to bigger fraction sizes of 4 Gy). Even this schedule failed. The radiation injury progressed more slowly when compared to the 70 Gy group, but the final outcome was very similar, i.e. total or nearly total injury by 12 mths after treatment.

There is no universally accepted radiological grading system for acute or late radiation-induced lung injury. Two recent reports [17, 18] have used a scoring system taking into account the intensity of radiological changes seen by chest radiographs, as well as the area involved. In our study we have used a modification of this method, where the intensity of injury was defined as the degree of loss of air-containing lung tissue as observed on chest radiographs, using a scoring system ranging from normal lung tissue to total lack of normal lung tissue. As radiation injury became severe, to the extent that normal anatomical structures and boundaries could no longer be differentiated, we approximated the affected areas as a percentage of the total area of the irradiated, shrinking lung.

Pleural mesothelioma spreads by local extension over serous surfaces [19]. Some of the changes interpreted as radiation injury on chest radiographs in this study may have been caused by the mesothelioma. We always read the lateral films to minimize the error caused by tumour growth into the interlobar pleura. Typically, radiation injury was rapidly progressive and patchy as opposed to the slowly growing and morphologically well-defined mesothelioma. This made differential diagnosis possible on serial radiographs. With severe radiation injury affecting the whole lung it was impossible to evaluate the extent of the mesothelioma on chest radiographs: CT is needed for this purpose.

All the patients were treated at our institution and, thus, we had laboratory and clinical data available in addition to repeated radiological assessments. Without this additional information the exact diagnosis of pneumonias would have been difficult, especially when the radiation injury was advanced (grade IV–V). Large collections of pleural fluid, cardiac decompen­ sation and pulmonary parenchymal metastases have fairly characteristic radiological manifestations and are easily diagnosed. Seven patients in our series had a mild degree of loss of air content on the chest radiographs prior to radiotherapy. In one patient the reason was mild pulmonary fibrosis; in the other cases the abnormal findings were interpreted as postoperative changes.

Twenty eight out of the 46 patients in this series received chemotherapy between surgery and hemithorax irradiation. Several chemotherapeutic agents are known to cause pulmonary toxicity and/or interaction with radiation [5, 20–22]. In our series, the preceding chemotherapy may have added to the lung injury.

As this was not a randomized study it was not possible to evaluate the various radiotherapy schedules as beneficial (or harmful) in terms of quality of life or survival. All patients experienced coughing and in most cases also dyspnoea after hemithorax irradiation, but these symptoms occur also in progressive pleural mesothelioma [23, 24]. Lung function was monitored in the high-dose (55 Gy, 70 Gy, 35+36 Gy) treatment groups (data not shown). The observed deterioration in lung function was compatible with total loss of function of the irradiated side [25], but it could not be consistently correlated with the changes seen on chest radiographs [25].

As long as we cannot cure or prevent radiation pneumonitis or fibrosis in humans once radiotherapy has been administered, there is no rationale for routine radiological monitoring of these events. We recommend the following time-schedule for chest radiographs for the assessment of radiation-induced lung injury in research protocols: pretreatment (reference), 2 mths ("pneumonitis"), 6 mths ("fibrosis") and 12 mths (final magnitude) following irradiation, with additional CT scans as required for differential diagnosis.

References


Appréciation par le cliché radiographique des lésions pulmonaires consécutives à une irradiation hémithoracique pour un mésothéliome pleural. P. Maasilta, L. Kivisaari, L.R. Holsti, L. Tammilehto, K. Mattson.

Nous avons étudié 235 clichés thoraciques de 46 patients atteints de mésothéliome pleural et soumis à une irradiation hémithoracique selon un des quatre régimes suivants: I: 20 Gy; II: 55 Gy; III: 70 Gy avec hyperfréquence; IV: 35 Gy avec hyperfréquence, suivis d'un hyperfréquence local de 36 Gy, afin de caractériser la nature, l'étendue et le déroulement des lésions pulmonaires induites par les rayons, et d'évaluer l'utilité de clichés thoraciques en série pour cette appréciation. L'atteinte pulmonaire au cliché thoracique a été quantifiée au stade 0 (aucune) au stade V (maximale), en se basant sur le degré de perte de tissu pulmonaire aisé. Des modifications de grade I ont été observées un à deux mois après la radiothérapie dans les régimes II-IV. La lésion de grade V s'est développée chez tous, sauf 3/4 patients du groupe à 20 Gy de 6 à 12 mois après l'irradiation. L'étendue et le déroulement des lésions pulmonaires induites par l'irradiation ont pu être définis par l'étude isolée de clichés thoraciques en série. En outre, la documentation de l'état tumoral et/ou des infections associées a nécessité des techniques d'imageur complémentaires ou des investigations de laboratoire, en particulier quand les stades IV et V de lésions pulmonaires étaient présents. Pour les protocoles de recherche évaluant les lésions pulmonaires induites par les rayons, des clichés thoraciques systématiques sont recommandés aux périodes suivantes: avant traitement et 2, 6 et 12 mois après traitement, en y adjoignant des CT scans lorsque le diagnostic différentiel l'imposait. *Eur Respir J.*, 1991, 4, 76-83.