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RADIOTHERAPY

Extra-pleural pneumonectomy in the era of image-guided intensity-modulated radiotherapy

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Abstract

Purpose To assess the outcome of malignant pleural mesothelioma patients treated with extra-pleural pneumonectomy (EPP) and adjuvant radiotherapy (RT), using the most advanced radiotherapeutic techniques, namely image-guided intensity-modulated RT (IG-IMRT).

Methods and materials Fifty-four patients were analyzed. Minimum radiation dose was 50 Gy (2 Gy/fr). Planning target volume encompassed the entire hemithorax, including the ipsilateral mediastinum if interested by disease, the pericardium and diaphragm, and any drain sites. The study endpoints included loco-regional control (LRC), distant metastases free survival (DMFS), and overall survival (OS), as well as radiation-related toxicity.

Results Major patients and treatment characteristics were the following: median age 62 years, epithelioid histology in 51 (94%) cases, locally advanced disease in 41 (90%) cases, and metastatic mediastinal lymph nodes in 27 patients (50%). Only 7 patients (13%) had gross residual disease after surgery. Chemotherapy was administered in 38 patients (70%). Median follow-up was 16 months (range 0–73 months). Median and 2-year OS were 21 months and was 43.8%, respectively. The predominant pattern of failure was distant: 34 patients (62.9%) developed some component of distant failure, and only 5 patients (9.2%) developed an isolated loco-regional recurrence. The estimates of LRC and DMFS at 2 years were 63.4% and 43.4%, respectively. Three fatal pneumonitis were documented. Other major toxicities included: Grade 2 and 3 pneumonitis in 1 and 2 cases, respectively, 1 case of bronchial fistula, pleural empyema, and Grade 3 esophagitis, respectively.

Conclusions Although executed in the era of high-technology radiotherapy (IG-IMRT), EPP should not be routinely performed.

Keywords Malignant pleural mesothelioma · Image-guided IMRT · Extra-pleural pneumonectomy

Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer, strictly correlated with asbestos exposure. It usually arises from the pleural surface with a high propension for local diffusion and nodal involvement, while distant metastases are a less frequent occurrence at diagnosis. Its prognosis is usually poor, with a median survival of 6–8 months in untreated patients [1].

Extra-pleural pneumonectomy (EPP) represents an aggressive surgical approach that has been shown to increase survival as part of a trimodal therapeutic strategy including adjuvant chemotherapy and radiotherapy. Sugarbaker et al. reported a 5-year survival of 46% in selected patients, including who had an epithelial histology, with negative resection margins and without metastatic extra-pleural nodes [2]. Due to these results, in recent years such surgical approach fell out of favor among the scientific community, mainly due to the severe perioperative stress, the noticeable complication rate, and the long-term detrimental anatomical and functional effects [3]. A less invasive approach, as lung-sparing surgery, found place particularly after the publication of the MARS trial, a feasibility study in which patients were randomized to receive EPP or not [4]. The median survival rate was 14.4 and 19.5 months for EPP group and the non-surgical group, respectively ($p=0.016$). In a meta-analysis comparing EPP with lung-sparing surgery, it was documented that pleurectomy/decortication might be performed

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with lower morbidity and mortality than EPP while resulting in comparable long-term survival [5]. However, the comparison of both procedures has several limitations and the choice for a specific therapy is still highly individual based on the extension of the disease, the patient comorbidities, and the center experience.

Also, the role of adjuvant radiotherapy (RT) was questioned after the recent publication of the SAKK trial, a randomized trial that failed to show a clinical advantage of adjuvant RT following EPP [6]. It must be underlined that in this study different fractionation schemes and RT techniques, including 3D conformal RT, were adopted.

Considering the uncertainties of the published literature, we conducted the present study to assess the outcome of MPM patients treated with EPP and adjuvant RT, using the most advanced radiotherapeutic techniques, namely image-guided intensity-modulated radiation therapy (IG-IMRT), in major academic centers in our country.

Materials and methods

This is a retrospective studies including patient's data collected in prospective databases in four academic centers in Italy. Patients were all treated with postoperative IG-IMRT after EPP for MPM between 2003 and 2014. Each patient signed an informed consent form that was approved by each Institutional Review Board before entry into the registry.

In the study period, 66 patients were treated with EPP and adjuvant IG-IMRT for MPM. Ten patients were excluded from the study: 7 were lost at follow-up immediately after the completion of RT (were followed in other facilities), and 5 were treated with palliative radiation doses. The analysis was then conducted on 54 patients.

All patients underwent postoperative IMRT, with a minimum dose of 50 Gy, delivered at 2 Gy per fraction. Planning target volume (PTV) was generated adding an isotropic margin of 0.5 cm to the clinical target volume (CTV), which encompassed the entire hemithorax, including the ipsilateral mediastinum if interested by disease, the pericardium and diaphragm, as well as the thoracotomy scars and any drain sites, according to the technique proposed by the researchers from the MD Anderson Cancer Center [7]. IMRT was delivered with tomotherapy in 17 patients [8], using a volumetric IMRT technique in 27 patients [9], and static 7-field "sliding window" IMRT in 10 patients [10]. Cone beam CT or megavoltage CT scans were performed daily for each patient, in order to properly guide the radiation treatment.

Patients were followed at regular intervals to determine tumor status and presence of symptoms. Physicians evaluated clinical symptoms using the Common Terminology Criteria of Adverse Events, version 3.0.

Loco-regional (LRR) and distant relapses were assessed using chest–abdomen CT, which was performed every 4–6 months; FDG-PET/CT was added at the workflow in case of concerns of disease progression. LRR was defined as any clinical or radiographic recurrence in the chest wall (local) or in the regional lymph nodes (hilar, mediastinal, or internal mammary lymph nodes).

The study endpoints, including loco-regional control (LRC), distant metastases free survival (DMFS), and overall survival (OS), were estimated using the Kaplan–Meier method, starting from the date of completion of RT until death or the last available follow. The log-rank test (2-sided) was used to test the differences between subgroups (statistical significance was considered for $p < 0.05$). The effect of individual factors on OS was assessed through hazard ratios and a corresponding 95% confidence interval (CI), estimated using the Cox proportional hazard model. The hazard ratios for potential risk factors included age, sex, performance

Table 1 Patient, tumor, and treatment characteristics

Age, years	
Median	62
Range	43–77
Gender	
Male	39 (72%)
Female	15 (28%)
Performance Status sec. ECOG	
0–1	48 (89%)
2	6 (11%)
Side	
Right	21 (39%)
Left	33 (61%)
Histological subtype	
Epithelioid	51 (94%)
Non-epithelioid	3 (6%)
Stage	
I–II	5 (9%)
III–IVA	49 (91%)
Gross residual disease after surgery	
Yes	7 (13%)
No	63 (87%)
Radiotherapy schedule	
50–50.4 Gy/25 fractions	13 (24%)
54 Gy/27 fractions	25 (46%)
60 Gy/25–30 fractions	14 (26%)
Not completed	2 (4%)
Chemotherapy schedule	
Neoadjuvant	31 (57%)
Adjuvant	4 (7%)
Neoadjuvant/adjuvant	3 (6%)
Not delivered	16 (30%)

Fig. 1 Kaplan-Mayer estimates of overall survival of patients treated with extrapleural pneumonectomy and image—guided intensity modulated radiation therapy

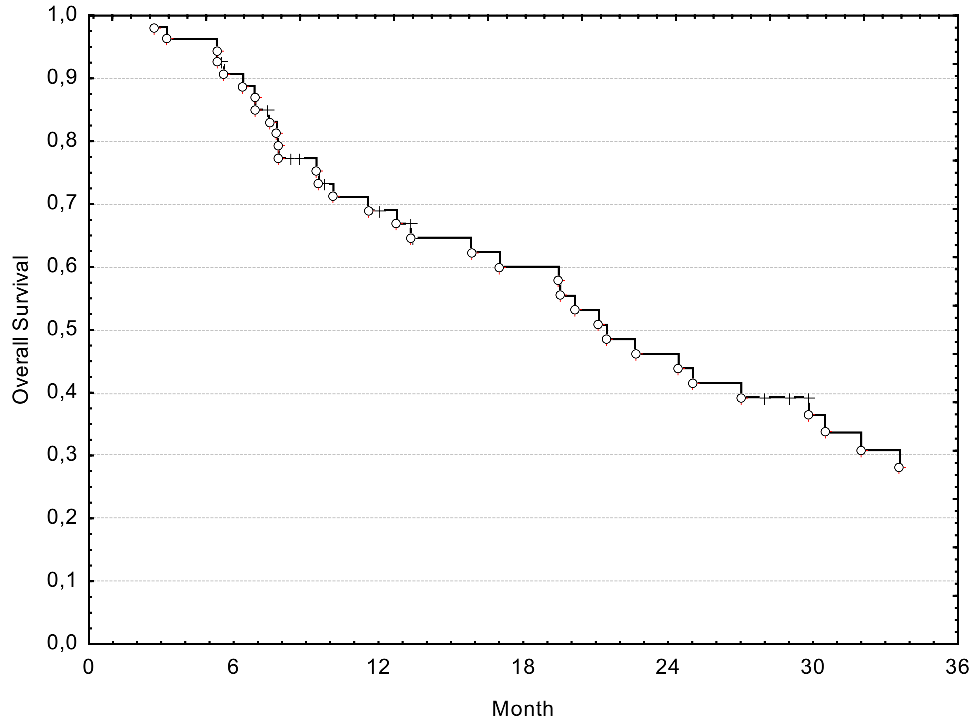

Table 2 Pattern of failure

Failure pattern	*n* (%)
Local	13 (24.0%)
Local only	4 (7.4%)
Local and nodal	1 (1.8%)
Local and distant	5 (9.2%)
Local, nodal, and distant	3 (5.5%)
Nodal	9 (16.6%)
Nodal only	0
Nodal and distant	5 (9.2%)
Distant	34 (62.9%)
Distant only	21 (38.8%)

status, histologic subtype, stage of disease, gross residual disease after surgery, and chemotherapy administration.

Results

Patients, tumor, and treatment characteristics are shown in Table 1. The median age was 62 years (range 43–77 years). Fifty-one patients (94%) had an epithelioid histology. Forty-nine patients (90%) had locally advanced (stage III–IVA) disease, and 27 patients (50%) had metastatic mediastinal lymph nodes. Only 7 patients (13%) had gross residual disease after surgery. Chemotherapy was administered in 38 patients (70%): 31 patients (57%) received neoadjuvant chemotherapy, 4 patients (7%) received adjuvant chemotherapy, and 3 patients (5%) received both neoadjuvant and adjuvant chemotherapy. The median number of chemotherapy cycles, consisting of cisplatin/carboplatin and pemetrexed, was 4 (range 3–7 cycles).

All patients underwent postoperative IMRT, with a total radiation dose ranging between 50 and 60 Gy in 25–30 fractions. IMRT consisted in radiotherapy started 30–40 days after the completion of adjuvant chemotherapy, or 2 months after surgery. RT was interrupted in two patients due to systemic progression of disease (and were included in the survival analysis). All the other patients successfully completed the radiation treatment.

With a median follow-up of 16 months (range 0–73 months), 38 patients (70%) died of disease, corresponding to an OS rate at 2 years of 43.8% and a median OS of 21 months (Fig. 1). The predominant pattern of failure was distant: 34 patients (62.9%) developed some component of distant failure, and only 5 patients (9.2%) developed an isolated loco-regional recurrence. The patterns of failure were recorded as composite failures and are listed in Table 2. Initial sites of distant failure were the following: peritoneum ($n=14$), lung ($n=10$), contralateral pleura ($n=6$), liver ($n=3$), and bone ($n=1$). The estimates of LRC and DMFS at 2 years were 63.4% and 43.4%, respectively (Fig. 2). We did not find any risk factor correlating with overall survival at the univariate analysis.

Three fatal (Grade 5) pneumonitis were documented within 6 months from the completion of radiotherapy. Other major

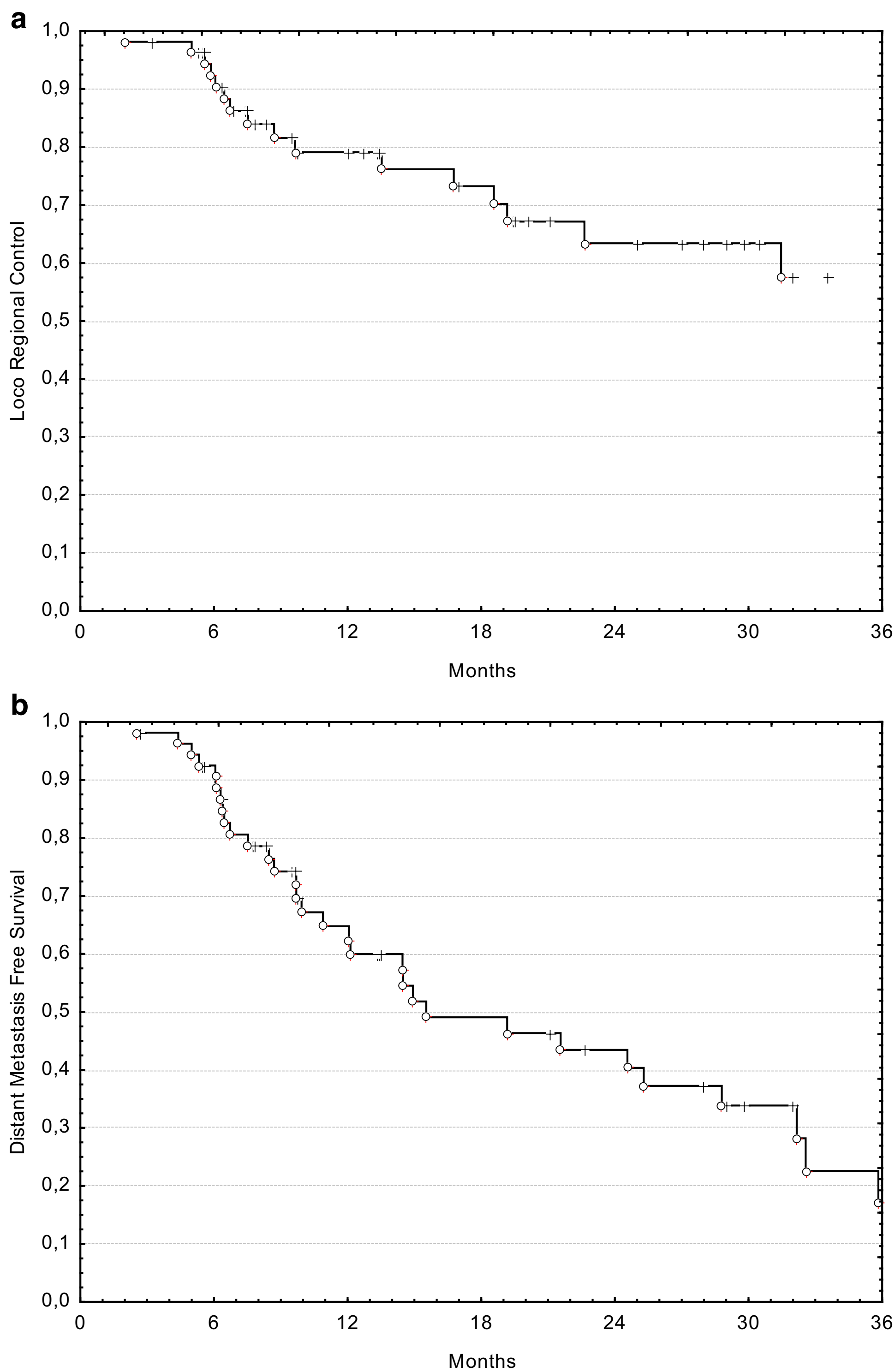

Fig. 2 Kaplan-Mayer estimates of loco-regional control (**a**) and distant metastasis-free survival (**b**) of patients treated with extrapleural pneumonectomy and image—guided intensity modulated radiation therapy

toxicities included: Grade 2 and 3 pneumonitis in 1 and 2 cases, respectively, 1 case of bronchial fistula, pleural empyema, and Grade 3 esophagitis, respectively. Nine patients reported severe fatigue.

Discussion

In the present paper, we wished to report the clinical outcome of MPM patients treated with EPP, followed by the

Table 3 Trimodality with extra-pleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma

Author	Year	No. of patients who completed trimodality therapy	Key results: median overall survival (months)	Key results: 2-year overall survival (%)	Predominant pattern of failure
Krug [13]	2009	40	29	61	Distant (65%)
Patel [14]	2011	30	23	50	Distant (60%)
Gomez [15]	2013	86	14	32	Distant (75%)
Thieke [16]	2015	62	20	42	Not reported
Present study	2018	54	21	43	Distant (63%)

most advanced radiotherapeutic treatment, namely image-guided IMRT, with the hypothesis that the adoption of such technology could lead to better clinical results. We actually failed to confirm this hypothesis: we reported a 2-year and a median OS of only 43% and 21 months, respectively. These results are particularly unsatisfying if considering that the patient population was selected positively: Only patients that successfully underwent EPP were included in the analysis.

It has been reported that almost 50% of patients who are suitable candidates for trimodality therapy actually complete the proposed treatment. Authors from the European Institute of Oncology reported that of the 83 patients candidate to chemotherapy, EPP, and RT, only 37 (45%) completed the planned trimodality treatment [11]. The 3-year OS was 48% for patients who completed the whole treatment compared with 14% for patients who did not undergo RT. De Perrot et al. reported that only 30 out of 60 patients completed high-dose hemithoracic RT after EPP; the median OS for all patients intended to undergo trimodality therapy was 14 months [12]. Similarly, a multicentric study conducted in USA on neoadjuvant chemotherapy followed by EPP and radiation reported that only 57% of the enrolled patients started radiation therapy [13]. The author documented a median OS of 17 months and 29 months in the intention to treat population and in the population that completed hemithoracic radiotherapy, respectively.

Our results are comparable with those published in the literature by the researchers from major academic centers in North America. The principal findings of these studies are summarized in Table 3.

In our study, only 5 (9.2%) patients experienced an isolated loco-regional failure, and predominant pattern of failure was distant: 62.9% of patients failed distantly. These data suggest that the high control rate obtained with extensive surgery and high-dose IG-IMRT did not translate into a survival advantage.

According to this, it has been showed that less aggressive therapeutic approaches, such as lung-sparing surgery followed by hemithoracic RT, might be suitable to manage a systemic disease such as MPM while guaranteeing an adequate rate of loco-regional control [17, 18].

The main limit of our study is a possible patient selection bias, as previously discussed. It is implicit that surgery-related toxicities and deaths were not considered in the present analysis, and patients who progressed immediately after surgery or chemotherapy were not enrolled in the study. On the other hand, these features highlight the poor results obtained in our study.

Taken together, our findings, including survival and pattern of failure, imply that EPP, although executed in the era of high-technology radiotherapy (IG-IMRT), should not be routinely performed. Probably, lung-sparing surgery represents a valid therapeutic option for MPM patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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