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INVITED REVIEW

Role of new radiation techniques in the treatment of pleural mesothelioma

Maurizio Amichetti[1], Stefano Lorentini[1], Sandro Tonoli[2] & Stefano Maria Magrini[2,3]

1 ATreP – Provincial Agency for Proton Therapy and Proton Therapy Unit, S. Chiara Hospital, Trento, Italy
2 Department of Radiation Oncology, Spedali Civili di Brescia, Brescia, Italy
3 Faculty of Medicine, University of Brescia, Brescia, Italy

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Correspondence
Maurizio Amichetti, ATreP – Provincial Agency for Proton Therapy and Proton Therapy Unit, S. Chiara Hospital, Via F.lli Perini 181, 38100 Trento TN, Italy.
Tel: +39 461 390409
Fax: +39 461 397728
Email: amichett@atrep.it

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Abstract

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm arising from the surface serosal cells of the pleural cavity. Surgery remains the main therapeutic standard in the treatment of MPM with the goal of complete gross cytoreduction of the tumor. Because MPM is a diffuse disease affecting the entire mesothelial lining of the hemithorax, surgery alone can rarely achieve adequate tumor-free resection margins. The surgical choices are pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP). Radiotherapy (RT) is usually applied postoperatively with the aim to improve local control. However, the efficacy of RT is limited by the large volume of the target to be irradiated (tumor and pleural cavity) and the radiosensitivity of the nearby organs (heart, liver, lung, spinal cord, and esophagus). These factors have historically limited the effective radiation doses that can be given to the patient. There is no role for radical RT alone, but the role of RT as part of multimodality therapy is discussed. After EPP adjuvant RT to the entire hemithorax can reduce the recurrence rate and is well tolerated if strict limits to the dose to contralateral lung are applied: the V20 and V5 (the percent volume of the lung receiving more than 20Gy and 5Gy of radiation) correlate with increased lung toxicity. The use of modern sophisticated techniques allows good target coverage, more conformal high dose delivery, and clinically relevant normal tissue sparing.

Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare, but aggressive, neoplasm derived from the mesothelial surfaces of the pleura; the disease is associated in most cases with asbestos exposure. Patients with MPM have a poor prognosis, with a median survival ranging from six to 18 months depending on the stage of the disease at the time of diagnosis.[1]

There is not a single best or standard approach for these patients, and with only a few prospective randomized studies on this topic, MPM remains a therapeutic challenge.[2] Despite aggressive single and multimodality treatments, MPM almost always recurs locally and the prognosis is still poor. The optimal treatment is mainly based on patient characteristics and clinical stage and may range from best-supportive care to multidisciplinary radical trimodality therapy (surgery, chemotherapy, radiotherapy).[3] Surgery is well accepted as a diagnostic modality and is also used to establish stage, provide palliation, and to offer cytoreduction.[4] Extrapleural pneumonectomy (EPP) has long been considered a radical intervention, however, this aggressive operation is fraught with significant morbidity, even at experienced centers, and many patients are not good candidates because of poor cardiopulmonary reserve or extent of disease.[5] A recent systematic review suggests that selected patients with MPM may benefit from EPP, especially when combined with neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy.[6] The recent published MARS study has, however, suggested that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.[7] Even after such a radical intervention, local recurrence after EPP can occur in up to 80% of patients.[8,9] When EPP is not feasible, less morbid procedures, such as pleurectomy/decortication (P/D), are performed, even though in most cases they do not permit a complete resection.[10] The P/D approach can have a curative intent only in stage I, while in clinical stages II-III it has to be

considered for palliation only.[11] A comparison between the two procedures suffers a bias of patient selection and there is no widely accepted data to show that one procedure is superior to the other in terms of survival.

Diffuse pleural involvement is common at presentation and, therefore, the results of surgery or radiation therapy (RT) alone are sub-optimal, with high local recurrence rates particularly in the ipsilateral chest.[12–15]

Radiotherapy is widely used in treating MPM, but supporting evidence is still scarce.[16] Hemithoracic RT to the chest cavity after EPP appears to decrease the risk of local recurrence,[17,18] but the role of postoperative RT is still a matter of debate.[19,20] More recently RT has been proposed after pleurectomy with intact lungs.[21]

Although MPM seems to be sensitive to radiation, its diffuse spread in the vicinity of many vital structures (heart, liver, lung, spinal cord, and esophagus) limits the optimal administration of adequate doses of radiotherapy.[22] Moreover, even after EPP, the diffuse nature of MPM and the manipulation of the exposed tumor during surgery puts the entire ipsilateral chest wall, diaphragm insertion, pericardium, mediastinum, and bronchial stump at high risk of local recurrence. These factors limit the effective radiation doses that can be given to the patient.

Conventional radiotherapy

Palliative radiotherapy

There is no clear evidence for the role of RT as palliative treatment in MPM. The dose required to obtain relief of symptoms varies according to different reports. Several fractionation schemes have been proposed: classical short-course schemes (20 Gy in 5 fractions or 30 Gy in 10 fractions)[22] or low-intermediate doses with conventional fractionation (40–45 Gy in 20–25 fractions)[23–25] with symptomatic response in up to 70% of cases. RT dose equal to or exceeding 40 Gy can offer adequate palliation, even though its duration is limited.

More recently, the role of palliative radiotherapy has been re-evaluated. Jenkins *et al*.[15] report their experience, pointing out that the results of palliative radiotherapy, using simple techniques and hypofractionation, were similar to those of chemotherapy. Moreover, they observed that patients responding to radiation had markedly prolonged survival, compared to those who did not (7.2 vs. 2.8 months, $P = 0.001$).

Adjuvant radiotherapy to the thoracic tracts

Patients with MPM are frequently subjected to procedures (thoracoscopy, positioning of drainage tube) in which the thoracic tracts could be the site for neoplastic cell diffusion in subcutaneous tissues, resulting in tumor seeding. Based on this observation, the irradiation of thoracic tracts was considered a useful tool as a prophylactic method to reduce the risk of neoplastic diffusion. In 1995, Boutin *et al*.[26] published the first randomized trial on this issue using a schedule of 21 Gy delivered in three days versus no irradiation, showing a reduction of the risk of developing neoplastic nodule (0% vs. 40%).

Other randomized trials with the same schedule[27] or of single dose radiotherapy (10 Gy with 9-Mev electrons),[28] to prevent procedure tract metastasis, showed no statistically significant differences in the incidence of tract metastasis.

At present, the role of prophylactic RT as interventionist treatment is still controversial. Evidence gained from studies reveals that it is of little use to patients treated with a multimodality approach, while it remains useful in patients who receive only supportive therapy.

Adjuvant conventional radiotherapy after surgery

MPM is an aggressive tumor with a tendency to spread to pleural surfaces, including pulmonary fissures and costophrenic recesses. As previously mentioned, a surgical approach with radical intent can include P/D, with preservation of lung or EPP, usually associated with ipsilateral hemi-pericardium and hemi-diaphragm resection and followed by pericardial and diaphragmatic reconstruction.

As elective indication P/D can consider only patients in stage I, while EPP is reserved for patients with clinical T1-3 N0 disease, in good general condition, and epithelioid histology. When EPP is not possible for absolute contraindications, P/D should be taken into account.[11]

Unfortunately, the incidence of local relapse after surgery is high, even if associated with chemotherapy, and it remains the first modality of failure,[14,29] underlining the importance of local control of disease as the main objective. For this reason adjuvant RT to the surgical bed was proposed.

The clinical target volume that should be treated with RT includes all surgically violated spaces, and the ipsilateral mediastinum, including the subcarinal areas. This represents a large and complex volume close to critical structures, such as spinal cord, heart, ipsilateral kidney, liver, and contralateral lung.

Until the 1980's, RT has been delivered in MPM only with palliative intent because of the impossibility of treating such large and complex treatment volumes with 2D techniques. In the following years, conventional 3D treatment techniques using photons +/– electrons[30,31] allowed treatment of large thoracic volumes, but without reaching high doses. The irregular shape of the hemithorax and mediastinum, the large volume of tissue being irradiated, and the adjacency to critical

structures, also limited the ability of tri-dimensional conformal RT (3D-CRT) to deliver sufficiently high doses without significant toxicity.

The most advanced technique in use before the advent of intensity-modulated radiation therapy (IMRT) was 3D-CRT adopted at the Memorial Sloan Kettering Cancer Center[17] and described in detail by Yajnik S *et al.*[32] After EPP, doses of 54 Gy were well tolerated (grade 0–2 fatigue, esophagitis), with the exception of one late esophageal fistula. The median survival was 33.8 months for stage I and II tumors and 10 months for stage III and IV tumors.

Allen *et al.*[33] reported the results obtained in 39 patients, treated with EPP between July 1994 and April 2004 at the Dana-Farber Cancer Institute/Brigham and Women's Hospital in Boston. With a median follow-up time of 23 months, the local failure rate was 50% after moderate doses (30–40 Gy) and 27% after high doses (54 Gy). In summary, the results obtained with conventional radiotherapy after EPP showed a significant reduction of local recurrences, in particular, when high doses (> 50 Gy) were delivered, even if the impact on overall survival was limited.

The use of conventional radiotherapy after P/D proved to be a non-effective treatment option for patients with MPM because residual disease cannot be eradicated with RT +/– brachiterapy.[34]

Trimodality treatment

The integration of the three principal therapeutic possibilities (surgery, chemotherapy, and radiotherapy) in an attempt to obtain better results than those achieved with single modalities has a long history. Since 1980, at the Brigham and Women's Hospital, EPP for malignant pleural mesothelioma has been integrated in the context of trimodality therapy.[35]

In 1999, Sugarbaker *et al.*[29] published the results of the treatment of 183 patients with pleural mesothelioma subjected to extrapleural pneumonectomy followed by adjuvant chemotherapy and radiotherapy. The perioperative mortality rate was 3.8% (seven deaths) and the morbidity 50%. The two and five year survival in the 176 remaining patients was 38% and 15%, respectively.

The role of modern radiotherapy techniques in the treatment of MPM after EPP

The efficacy of adjuvant RT in this context was impaired by the use of conventional RT techniques with poor capability to homogeneously cover complex target shapes with adequate doses and sparing proximal organs at risk (OAR), avoiding severe toxicities. The introduction of new RT delivery techniques in the 21st century has made the routine use of RT in the treatment of MPM easier.

Intensity-modulated radiation therapy (IMRT)

New irradiation techniques, such as IMRT, have been developed in an effort to increase the administered dose to targeted tissues, without reaching toxic doses for neighboring tissues. IMRT is a RT technique that utilizes computer-controlled linear accelerators to deliver very conformed radiation by modulating the intensity of the radiation beam in multiple volumes. This can result in an improved dose distribution and a higher dose in the target tissue, combining good local control with protection of OAR.[36]

IMRT has to be carefully planned by using 3D CT images of the patient in conjunction with computerized dose calculations to determine the dose-intensity pattern, making it a complex and time-consuming procedure.

Because of the successful incorporation of IMRT into the treatment of cancers in other anatomically challenging regions, such as prostate and head and neck, IMRT techniques were extrapolated to treat MPM.

The ability of IMRT to tightly conform radiation doses to large and complex targets and generate concave dose distributions and tight dose gradients makes it theoretically very suitable for post-operative RT after EPP.

Initial studies have shown IMRT after EPP to be feasible and able to deliver potentially curative doses to complex target volumes, such as the hemithorax, with acceptable doses to surrounding tissues.[18] Investigators at the MD Anderson Cancer Center (TX, USA), describing 100 consecutive patients who underwent EPP, reported that 63 of them treated with IMRT (total dose: 45 Gy) after EPP showed excellent local control, with a 13% local recurrence rate and acceptable acute toxicity. Only one patient experienced severe shortness of breath. This series suggested that IMRT after EPP is feasible, safe, and efficacious.

However, some other series of IMRT after EPP reported severe or lethal pulmonary toxicity. Data from Allen *et al.*[37] showed that six out of 13 patients treated with IMRT after EPP developed fatal radiation pneumonitis. This data led to significant concern about the safety of IMRT in the treatment of MPM.[38] Rice *et al.*[39] also reported six out of 63 patients developed fatal pulmonary toxicities within six months of IMRT. Further retrospective analyses, however, have demonstrated that IMRT pulmonary complications are associated with the dose of radiation delivered to the contralateral lung.[40] The V20 (the percent volume of the lung receiving more than 20Gy of radiation) for the contralateral lung was found to be the only independent determinant for risk of pulmonary-related death, implying that the V20 should be kept as low as possible after EPP.[39,41] While the series of Allen *et al.*[37] included a small group of patients, increased mean lung dose and V5, in addition to V20, appeared to correlate with severe pulmonary toxicity. When normal tissue con-

straints are more rigorously applied, IMRT use is associated with acceptable toxicity in patients with and without intact lungs.[39] New advances in technology can allow for lower doses to the contralateral lung, decreased treatment delivery time, and improved target dose coverage. It has been observed that with increasing experience, target volume coverage can improve and the dose to the contralateral lung can decrease, reducing the rate of pulmonary toxicity.[42]

In one retrospective series, patients received either adjuvant external beam radiation therapy (EBRT) or IMRT after EPP based on the preference of the treating radiation oncologist.[43] Those who received IMRT had significantly less local recurrence without increased complications, compared to those who received EBRT (14% vs. 42%).

A systematic review of the current evidence and indications for adjuvant IMRT has recently been published;[44] excellent local control can be achieved with its use after EPP. Severe pulmonary toxicity may be avoided by setting stringent dose constraints for the contralateral lung.

As a consequence of the above reported considerations, postoperative RT should be definitively considered as a component of multi-(tri)modality treatment in very select patients with localized disease. IMRT is potentially more effective than conventional radiotherapy in the adjuvant setting after EPP, as this could provide good local control and protect OAR. However, use of this technique cannot currently be recommended outside expert centers because of its potentially serious adverse effects. A review of the most relevant series reported in the literature with the use of trimodality is shown in Table 1.[37,40,43,45–56]

Helical tomotherapy and other advanced delivery techniques

Hemithoracic IMRT using helical tomotherapy has recently been proposed after EPP as a useful technique to treat such complex volumes as the pleural cavity. It seems to have better dose distribution than the "classic" IMRT, revealing the possibility of reducing the V5, in comparison with IMRT standard plans,[57] and to deliver a higher radiation dose with good homogeneity and coverage results.[47,58] An example of adjuvant treatment after EPP with tomotherapy is shown in Figure 1.

Another technique recently proposed is volumetric modulated arc radiotherapy (V-MAT): a dosimetric study[59] showed that compared with conventional IMRT, V-MAT demonstrated similar target coverage and better dose sparing to the organs at risk.

Modern RT techniques in MPM patients with intact lungs

In patients with MPM who are unable to undergo pneumonectomy, it is difficult to deliver radical radiation doses to the hemithorax after P/D or to the pleura in inoperable patients without significant toxicity. In order to overcome the constraints of patients with no previous pneumonectomy, the use of IMRT is now being explored. The same difficulties that radiation oncologists have addressed after EPP are perhaps more complex in these cases. For example, administering adjuvant RT with an intact lung is more difficult with IMRT treatment because of the need for the patient to breathe and the subsequent motion as a result.

Before the introduction of sophisticated new radiation techniques, the use of P/D with conventional radiotherapy plus brachytherapy showed that P/D with adjuvant RT is not an effective treatment option for patients with MPM.[34,60]

The irradiation of the circumferential pleural envelope with IMRT appears feasible, but the fact that this approach does not address the disease in the fissures is problematic.[38]

Rosenzweig *et al*.[61] reported the treatment of 36 patients (66% in Stage III-IV) with pleural IMRT to the hemithorax (median dose, 46.8 Gy; range, 41.4–50.4). Grade 3 or worse acute toxicity (pneumonitis) was observed in seven (20%) patients with one death. In 30 patients assessable for late toxicity, five had continuing Grade 3 pneumonitis. Median overall survival (OS) in patients who underwent surgery was 26 months, and in patients who did not undergo surgery, 17 months.

Fodor *et al*.[62] treated two groups of 12 patients each with progressive MPM, not eligible for resection with helical tomotherapy, at a dose of 56 and 62.5 Gy. The higher dose was able to obtain an increased median overall survival (eight vs. 20 months) and time to local relapse (eight vs. 17 months) and one-year local relapse-free rate (16% vs. 81%, $P = 0.003$).

In a retrospective cohort, 36 patients (20 with a prior P/D and 16 patients unresectable) were treated with pleural IMRT.[63] Twenty percent of patients experienced grade 3 or worse pneumonitis, although all but one patient recovered. The median survival for patients treated with or without P/D and pleural IMRT was 26 months and 17 months, respectively. The one and two-year OS rates were 80% and 55% and 75% and 21%, respectively.

Lang-Lazdunski *et al*.[46] used RT only on thoracic drains after P/D in the context of a "trimodal" approach with very similar results and low toxicity, in comparison to those obtainable in trimodal treatment with EPP.

At present, advances in radiation techniques have allowed the exploration of high-dose radiation therapy after P/D; pleural IMRT at a radical dose with intact lung is still under clinical evaluation and should preferably be considered, in our opinion, in the context of clinical trials.

Proton therapy

There is also some limited data comparing proton-beam radiation (PT) with IMRT following EPP. The main advantage

Table 1 Most recent series of patients with malignant pleural mesothelioma treated with a multi(tri-)modality approach

Author	Pts	Chemotherapy scheme (% of total n. of patients)	Surgery (% of total n. of patients)	HT chemoperfusion	RT technique and dose (% of total n. of patients)	Survival	Treatment mortality	Notes
Allen *et al.*[33]	39	Cisplatin concurrent; cisplatin/gemx2 before or after surgery; Carboplatin/paclx2 after surgery	EPP (100%)	15% cisplatin	3D-CRT 30 Gy/20fr. + boost 10–24 Gy or 39.6 Gy/20 fr. + boost 14.4 Gy (90%)	19 months 2 years36% 5 years 14%	8%	
Miles *et al.*[40]	13	NEOAD-AD Cisplatin/pem 12/13	EPP (100%)	–	IMRT 45 Gy/25 fr. (100%)	OS 1 year 46%	One patient died of fatal pulmonary toxicity	23% Grade 2 or greater acute pulmonary toxicity, one patient died from pneumonia
Bille *et al.*[45]	25	NEOAD Cisplatin/gem or pem x3	EPP (88%)	–	3D-CRT 54 Gy/30 fr. (68%)	Median 12.8 months 2 years 18.2%	18.2%	13% bronchopleural fistula RT toxicity: 1 fatal pulmonary embolus, 1 transverse myelitis
Lang-Lazdunski *et al.*[46]	25	NEOAD cisplatin/gem or pem x3	EPP (88%)	–	3D-CRT 54 Gy/30 fr. (68%)	Median 18.2 months 1 year 54.5% 2 years 18.2% 5 years 9%	4.5%	RT complications (68%): 1 fatal pneumonia, 1 fatal pulmonary embolus 68%
Sylvestre *et al.*[47]	24	NEOAD carboplatin/pem x3 (54%)	EPP (96%)	–	Tomotherapy 50 Gy/25 fr. + boost for high risk regions (57.2 Gy) (96%)	2 year DFS 51.8%	8%	2 patients Grade 3 pneumonitis
Bölükbas *et al.*[48]	35	AD cisplatin/pemetrexed x4	P	–	21 Gy/3 fr. or 50.4 Gy/28 fr. (93.5%)	Median OS 30 months 1 year 69% 2 years 50% 3 years 31%	5.8% toxic death for surgery and chemotherapy	33% of patients completed the protocol
Buduhan *et al.*[43]	46	NEOAD cisplatin/pem x4 or cisplatin, methotrexate, vinblastine	EPP (100%)	–	14 3D-CRT/24 IMRT (82%)	Median OS 24 months 1 year 69% 2 years 50% 3 years 31%	4.3%	Minor postoperative morbidities: 54%
Kristensen *et al.*[49]	26	NEOAD cisplatin-based combination x3-6	EPP	–	3D-CRT or IMRT 50 on CTV 60 Gy on residual disease or close/positive margins or 54 Gy/30 fr.	Not reported	19%	15% grade 5 lung toxicity
De Perrot *et al.*[50]	60	NEOAD cisplatin based x2-3	EPP (75%)	–	50/60 Gy (50%)	Median OS 14 months (all patients Intention to treat), 5 years 10% DFS 53% in N0	9%	
Yamanaka *et al.*[51]	40	NEOAD cisplatin + pem X3	EPP (100%)	–	3D-CRT 54 Gy/30 fr.			Results not yet available

Table 1 Continued

Author	Pts	Chemotherapy scheme (% of total n. of patients)	Surgery (% of total n. of patients)	HT chemoperfusion	RT technique and dose (% of total n. of patients)	Survival	Treatment mortality	Notes
Weder *et al.*[52]	61	NEOAD Cisplatin + gem x3 (95%)	EPP (74%)	–	50/60 Gy (61%)	Median OS 19.8 months (all patients Intention to treat), 23 months (operated) 1 year 67% 2 years 44% 3 years 22%	2.2%	35% major post-operative complications
Rea *et al.*[53]	21	NEOAD carbo + gem x3-4 (50%)	EPP (81%)	–	3D 45 Gy + boost 10–14 Gy to high risk areas, no IMRT	Median OS 25.5 months; patients completing all treatment: 33 months 1 year 71% 2 years 33% 5 years 19%	0%	Total morbidity 52.4%
Krug *et al.*[54]	77	NEOAD cisplatin/pem x4 (83%)	EPP (77%)	–	54 Gy/30 fr. (54%)	Median OS: 29.1 months (patients completing all treatment); 13.9 months (stable or progressing) 2 years 61.2%	6.5%	40% patients completed the whole treatment. Radiation pneumonitis 2 patients (one death)
Van Schil *et al.*[55]	57	NEOAD cisplatin/pemx4 (95%)	EPP (76%)	–	54 Gy IMRT 14 patients, 3D-CRT 24 patients (64%)	Median OS 18.4 months 1 year 70.2% 2 years 33% 5 years 19%	6.5%	Reoperation rate: 15%
Tonoli *et al.*[56]	56	NEOAD 20 patients (35.7%) AD 25 patients Cisplatin-pem (44.6%)	EPP (100%)	cisplatin (30.4%)	50 IMRT 50 patients 50 Gy/25 fr., 60 Gy (20 patients) if positive margins	3 years DSS 62% 3 years LC 90%	2 patients possibly as a result of RT	

3D-CRT, threedimensional conformal radiation therapy; AD, adjuvant; D, decortication; DFS, disease-free survival; DSS, disease specific survival; EPP, extra pleural pneumonectomy; fr., fractions; gem, gemcitabine; Gy, Gray; HT, hyperthermic; IMRT, intensity modulated radiation therapy; LC, local control; NEOAD, neoadjuvant; OS, overall survival; P, pleurectomy; pacl, paclitaxel; pem, pemetrexed; RT, radiation therapy.

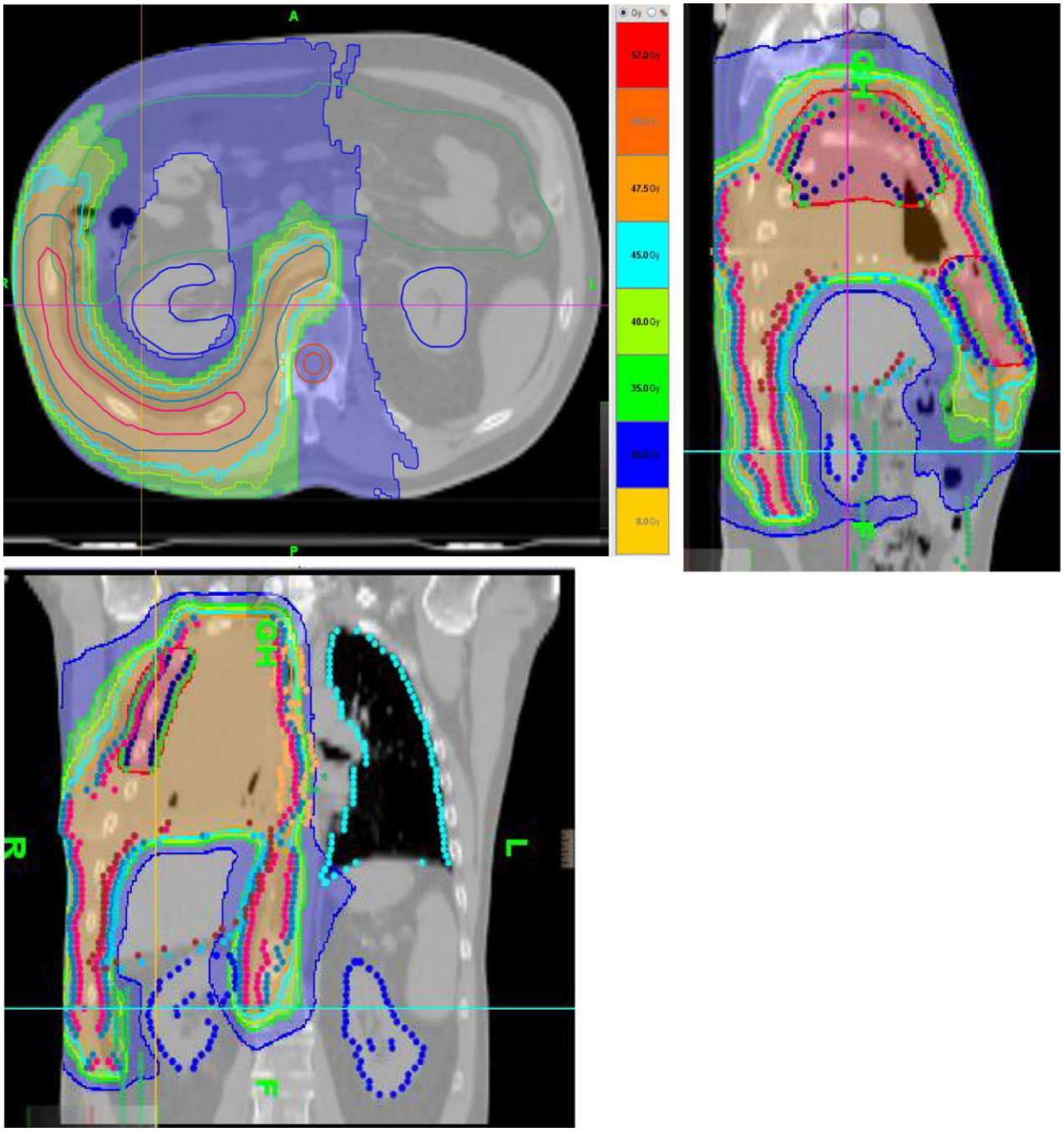

Figure 1 Typical dose distribution obtained using HiART tomotherapy in a patient subjected to right extrapleural pneumonectomy (EPP) for pleural mesothelioma with positive margins to the chest wall in two sites (treated with simultaneous integrated boost of 60 Gy).

of PT is the ability to localize the radiation dosage more precisely when compared with other types of external-beam radiotherapy. Because of their large mass, protons have little lateral side scatter and finite range, along with the capability to release no dose beyond the distal fall-off. The main dosimetric advantages of protons rely on the possibility of obtaining dose distributions more conformed to the target volume, while minimizing (or in some cases avoiding completely), the undesired dose received by the healthy structures located in the target proximity,[64] with the potential resulting clinical benefits. Until now, many different anatomical sites characterized by a high degree of complexity from the planning standpoint have been treated with protons.[65] Although in use for over 40 years, the efficacy of this radiation technology for different

tumor types is still controversial. In that respect, as the new delivery technologies (i.e. active scanning based techniques) allow for an improvement of the dose delivery (e.g. better dose shaping than scattering technique, easier intensity modulation, dose repainting, etc.), an increasing number of sites potentially suitable to be treated with protons will be studied.

In the literature only few papers are dedicated to this issue[66,67] and some[56,68,69] address the possible application of proton therapy in the case of MPM, suggesting that the role of PT is promising both from the point of view of the coverage of the tumor and for the sparing of OAR.

Dosimetric considerations have been made in two recently published planning studies.[66,67] These are the only studies where a quantitative dosimetric analysis of PT application in MPM has been carried-out. Both studies simulate proton plans (with pencil beam scanning) and compare them with IMRT treatments.

In the first article by Krayenbuehl *et al*.,[66] results from eight patients were retrieved, which showed a statistically significant sparing of OAR, such as the liver, contralateral lung, ipsilateral kidney, and heart, with the use of protons. Regarding the target coverage, they scored a statistically significant improvement of the main target volume coverage, with a V95 (volume of target receiving 95% of prescription dose), 1.6% larger with protons in respect to IMRT, as well as an improved dose conformity and homogeneity.

The latter study by Lorentini *et al*.,[67] reports a dosimetric comparison along with a normal tissue complication probability (NTCP) assessment over seven MPM cases. These cases were re-planned in the same planning software, both with photons (static-IMRT) and protons, by using an intensity modulated (IMPT) technique. The "standard" dosimetric analysis resulted in similar findings in comparison with the data of Krayenbuehl *et al*. NTCP analysis revealed a statistically significant superiority of IMPT plans over IMRT for liver, with an NTCP reduction of 31.2%, esophagus (NTCP 16.5% lesser), and especially for ipsilateral kidney (80% lesser).

On these bases, the use of PT for the treatment of MPM could be considered, in the frame of a trimodality approach, as an alternative technique for the management of this disease, in respect to the other techniques currently available on the radiation therapy scenario.

Conclusions

Radiotherapy is considered an accepted treatment for MPM in the context of multimodal therapy in patients with limited stage of disease or as a useful tool for the treatment of inoperable cases. A combined (tri-)modality approach is only recommended for carefully selected patients with localized disease. Because of the high associated morbidity and mortality, this treatment should only be performed in expert centers, preferably in a clinical trial setting.

Radiation to the pleural cavity using any new available technology remains complex, mainly as a result of complex target shape and delineation, close proximity of OARs to areas needing treatment, and the need for relatively high-dose delivery.

The use of modern conformal techniques (like IMRT) seems to have gained an important clinical role. The increase in clinical experience, especially in the context of carefully documented clinical trials, could help take advantage of other recently introduced techniques. The search for a possible therapeutic gain for this severe disease is surely worthwhile, and, therefore, more clinical and experimental data is urgently required.

Disclosure

No authors report any conflict of interest.

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