Radiotherapy Treatment for Malignant Pleural Mesothelioma

Heading

Neoplastic pathologies are treated using different approaches depending on the stage of the disease; hence, there are early-stage tumours attacked by radical therapies, such as, for example, surgery and radiotherapy, and there are advanced-stage or metastatic tumours which are usually treated with palliative therapies, such as chemotherapy, immunotherapy or radiotherapy.

Malignant Pleural Mesothelioma (MPM) generally has an unlucky prognosis, and it is usually diagnosed at a late phase, when the disease is already in an advanced stage and cannot be subjected to radical treatment through a surgical approach. Therefore, most patients affected by MPM are treated with systemic chemotherapy or experimental protocols, which have nevertheless a merely palliative purpose, in addition to aiming at making the disease a chronic one for as long as possible.

However, radiotherapy also plays a role in the treatment of MPM, and can be used in different settings and even for opposite purposes.

This bibliographic review aims to evaluate the last studies published in scientific reviews which investigate the role of radiotherapy in the treatment of MPM.

Introduction

MPM is considered to be a radiotherapy-resistant neoplasia. Indeed, several studies have shown minimum benefits of this approach combined with the other standard treatments usually implemented in this area[1]. Moreover, very often the use of radiotherapy is postponed due to the significant toxicity which this treatment can have on the lung itself.
In fact, a common collateral effect is represented by post-actinic pneumonias[2]. Already back in 1991,

studies were published highlighting the pulmonary toxicity caused by radiotherapy applied at the level of the entire hemi-thorax: this data underscores how this treatment entails a moderate-severe and irreversible pulmonary damage in most patients subjected to radiotherapy[3].

Therefore, radiotherapy has been mainly considered within the setting of palliative treatments, such as, for example, pain management[4].

However, recent publications have determined that this recommendation should be changed as it has been observed that patients subjected to radiotherapy for palliative purposes also showed a good response depending on the administration of specific dosages[5].

In vitro studies were also conducted assessing the usefulness of radiotherapy on the cell lines of malignant mesothelioma[6]. This data described the cellular sensitivity of mesothelioma to radiotherapy treatments, and it was shown that after two dosages of 2 Gy of radiation were administered, about 60-80% of the mesothelioma cells suffered a damage resulting in the inability to generate new colonies[7].

With regards to this, experiments were also carried out on cell lines of murine models, which have demonstrated cellular survival in only 10% of the cases after 5 Gy of radiotherapy were administered[8].

It is interesting to observe that some authors also proved the existence of a systemic activation and an increase in the proliferation of immune system cells (T-cells), in murine models in which cells previously irradiated in vitro with 5-15 Gy were injected under the skin[9].

If this research conducted on murine cells is applied to human cells, we can observe that sensitivity to radiotherapy is closely dependent upon the histological sub-type of the MPM. For instance, administering 25 Gy in vitro determines an increase in the release of damage signals, such as, for example, HMGB1 (High Mobility Group box 1), especially in the case of epithelioid MPA cells and not of sarcomatoid MPA cells. Since the release of HMGB1 is considered a pro-inflammatory factor able to activate dendritic cells and induce an immunotherapy response against the tumour, the absence of HMGB1 in sarcomatoid MPM might explain the different sensitivity of the two histological subtypes to radiotherapy[10].

Medicines that act on the cell cycle could increase sensibility to radiotherapy, and this was tested on MPM cell lines MPM[11 12 13]. Indeed, the radiotherapy treatment causes damage at the DNA level through the generation of oxygen free radicals, consequently causing the cells to die[14 15]. Treatments that inhibit DNA repair or increase death of the cells therefore work in synergy with the radiotherapy.

In this case as well, however, the data is inconsistent since this was observed above all in the epithelioid MPM cell lines and not in sarcomatoid MPM cell lines. This difference may be tied to the fact that sarcomatoid tumours have such a resilience that allows them to better defend themselves against the DNA damage due to the sarcomatoid histotypes. Another explanation for the resistance of the sarcomatoid phenotype seems to be tied to the influence of the expression and of the release of fibroblasts growth factor[16].

Prophylactic radiotherapy

In the case of surgery or surgical diagnostic procedures, there may be a dissemination of tumour cells at the level of the site where said approach was implemented.
The risk of local dissemination during a biopsy increases with the size of the procedure and ranges from 10% in case of transparietal biopsy, 13% in case of pleuroscopy, up to 26% in case a thoracotomy is performed[17].
The metastasised tract may cause serious problems not only related to the worsening of the stage and of the prognosis, but also in terms of quality of life, since it can be the cause of several symptoms, the most frequent of which is pain.
For this reason, prophylactic therapy plays a role in these patients, since it reduces the risk of metastasis resulting from these diagnostic or therapeutic procedures.
The initial data pertaining to these findings was published in 1995; the authors proved that a reduction in this dissemination could be tied to the reduced angiogenesis and to the diminished release in tumour growth factors which occur thanks to the use of radiotherapy treatment[18].
Nevertheless, this data is inconsistent, since other studies have not confirmed this research and, on the contrary, have shown a difference in terms of reduction of the risk of metastasis after an invasive procedure, between the group of patients treated with radiotherapy and the control group[19 20 21 22 23 24 25 26].

Palliative radiotherapy

We speak of palliative radiotherapy for patients suffering from MPM when the treatment is aimed, for example, at the management of pain, of dysphagia, of obstruction of the upper respiratory tract and at relief of vena cava compression[27]. In fact, the radiotherapy treatment is able to bring about an improvement in severe symptoms for the patient and, although this setting does not entail an increase in survival, it is nevertheless an effective method for improving the quality of life.
Actually, radiotherapy can be used for palliative purposes also for the remote treatment of metastasis, such as, for example, bone or encephalic lesions. In this case, radiotherapy aims at blocking the secondary lesion, improving any symptoms that may be present, as wells as at reducing any symptoms and signs that may develop in the future due to these metastases, and that may lead to a further worsening of the patient's quality of life[28 29 30 31].
In fact, it has been demonstrated that, especially for non-sarcomatoid histology, palliative radiotherapy was useful and that sensitivity to radiotherapy was correlated to an improvement of the patient's overall conditions and, consequently, a clear clinical benefit[32 33 34].

Adjuvant radiotherapy

Adjuvant radiotherapy is the treatment administered after surgery as an “adjuvant” to the surgical approach in order to obtain the best outcome.

The Memorial Sloan Kettering Cancer Center (MSKCC, New York City, NY, USA) was a pioneer in the study of this technique[35 36 37 38 39 40].

The radiotherapy approach may also be used intra-surgery. However, it was demonstrated that this option is not an effective treatment and, moreover may cause severe complications such as pleural empyema[41 42 43].

The use of hemithoracic adjuvant radiotherapy at high dosages seems to entail a reduction in the risk of relapse; in fact, some authors claim that with this treatment, the risk of locoregional relapse is approximately 15%[44 45 46].

Intensity-modulated radiotherapy (IMRT) has also been used as hemithoracic therapy at high dosages, and it has shown to provide a benefit in terms of relapse reduction, especially when applied at the level of the base of the ribcage, in areas with a higher risk of a relapse of the locoregional disease[47 48 49].

It is important to remember that these treatments are not risk-free. For example, the literature includes cases of lethal contralateral pneumonia, especially after use of radiotherapy after an extrapleural pneumonectomy[50 51 52]. For this reason, a crucial factor is the proper dosage of the radiotherapy in addition to a careful evaluation of the patient’s respiratory functionality[53 54 55].

Other authors, on the other hand, have demonstrated how radiotherapy, and in particular the modulated-intensity type, may be an approach that is easily tolerated by patient and featuring a not-so-high risk of post-actinic pneumonias[56 57 58 59 60 61 62].

Moreover, a more innovative technique would allow a further reduction in the risk of complications: this innovative technique is called VMAT (Volumetric-Modulated Arc Therapy)[63 64 65].

Increased control over the disease has been described in patients subjected to adjuvant radiotherapy[66 67]. With these purposes, new randomised and prospective studies on the association between chemotherapy and adjuvant radiotherapy may possibly provide data demonstrating greater efficacy[68 69 70 71 72 73 74]. Indeed, chemotherapy may reduce the risk of a relapse while radiotherapy may increase local control[75 76 77 78 79 80 81 82 83 84 85 86].

Induction radiotherapy

Trimodal therapy consists of the application of chemotherapy, followed by extrapleural pneumonectomy and by hemithoracic adjuvant radiotherapy at high dosages.

Use of the therapy in this setting resulted in better survival and local control of the disease[87]. On the basis of this research, we can hypothesise that radiotherapy can also be applied at the early stages of MPM, rather than using chemotherapy: this therapy setting is known as "induction" radiotherapy[88 89].

In studies on the application of radiotherapy in this setting, the surgical complications which occurred after the induction radiotherapy treatment were similar to those recorded after the adjuvant chemotherapy treatment[90].

In this case too, the patients with epithelioid MPM had a better outcome compared to those affected by the other histological type[91] .

Several studies have underscored how the tumour volume is correlated with the outcome and how it could also be a guiding factor in the choice of whether or not to subject a patient to induction therapy[92 93 94 95]. On the contrary, the same data cannot be applied to the response to chemotherapy, which instead does not depend on the volume of the neoplasias, as it happens with radiotherapy and surgery[96]. This data indicates that patients with localised disease may be good candidates for treatment with induction radiotherapy, whilst those with a large-sized tumour would benefit instead from chemotherapy[97].

Conclusions

Future prospects include the possibility to combine standard treatments for MPM, such as radiotherapy, and immune-system treatments[98 99 100]. In the past fifteen years, the role of radiotherapy in the treatment of MPM has grown, also supported by scientific evidence demonstrated in various treatment settings.

However, the real benefit of this method has yet to be completely defined for this type of neoplasia, but new and innovative approaches, such as IMRT at the pleural level and induction-accelerated hemithoracic radiotherapy performed after surgery may very well be feasible and well-tolerated.

New studies will make it possible to provide an answer these still unanswered questions.

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