Editorial

Non-ablative hypofractionated hemithoracic radiation—a new standard of care in mesothelioma?

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Provenance: This is an invited Editorial commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Winterthur, Switzerland).
Comment on: Parisi E, Romeo A, Sarnelli A, *et al.* High dose irradiation after pleurectomy/decortication or biopsy for pleural mesothelioma treatment. Cancer Radiother 2017;21:766-73.

Submitted Sep 16, 2018. Accepted for publication Sep 25, 2018.
doi: 10.21037/jtd.2018.09.131
View this article at: http://dx.doi.org/10.21037/jtd.2018.09.131

The role of radiation therapy in malignant pleural mesothelioma (MPM) has been explored for the past 50 years. Originally, MPMs were thought radioresistant tumors. However, experimental evidence suggested otherwise (1). For instance, *in vitro* studies have shown that mesothelioma cell lines were more sensitive to radiation than non-small cell lung cancer cell lines, experiments in mice models of mesothelioma have shown response to radiation therapy, clinical studies have demonstrated benefit of radiation in the palliative setting when specific areas of the chest were targeted, and hemithoracic radiation have shown good local control when combined with radical surgery [see review in (1) for specific references].

While palliative radiation has been delivered with hypofractionated regimen of at least 3 Gy per daily fraction, normofractionated doses (2 Gy per daily fraction) has typically been used in the setting of conventional hemithoracic radiation. The publication from Parisi and colleagues with accelerated hypofractionated hemithoracic radiation in the adjuvant setting after pleurectomy-decortication (PD) or tumor biopsy as well as our experience with accelerated hypofractionated hemithoracic radiation in the induction setting raise the question as to whether hypofractionated rather than normofractionated radiation should be used for hemithoracic radiation (2,3).

Hypofractionated radiation has several advantages. It can be completed over a few days rather than a few weeks; it can be delivered in the induction or the adjuvant setting in combination with radical surgery; for a given total dose, it delivers much greater biological effect (compared to normofractionation); and, perhaps more importantly, it may provide a specific activation of the immune system directed against the tumor that could provide a platform for immunotherapy (4). However, this is generally at the cost of increased complexity in radiation planning and delivery due to increased requirements for treatment precision and accuracy as well as potentially more normal tissue toxicity within the high dose irradiated volume. The optimal hypofractionated regimen, however, remains to be determined in mesothelioma. The dosage and fractionation have been different depending on the indications.

Hypofractionated radiation has successfully been used for palliation in cases of mediastinal compression or intractable pain related to tumor invasion into the chest wall or the spine. Current evidence suggests that 4 Gy per fraction is the minimal dose to achieve a response and most centers currently recommend 20 Gy in 5 fractions for palliation in mesothelioma (5,6). A prospective phase II study (SYSTEMS) using 20 Gy in 5 fractions demonstrated that 14 out of 40 patients (35%) had improvement in their pain at 5 weeks after radiation and that 5 patients (12.5%) had complete pain resolution (7). This trial led to a multicenter phase II randomized dose escalation study (SYSTEMS-2) to determine if a higher dose of radiation of 36 Gy in 6 fractions over 2 weeks could provide additional benefit on pain control compared to 20 Gy in 5 fractions over 1 week. This study dose fractionation is supported by a retrospective study demonstrating that palliative radiation with 36 Gy

in 12 fractions provided radiological response by modified RECIST criteria in up to 43% of the patients (8).

Prophylactic irradiation of surgical port sites is another area where hypofractionated radiation has been used to reduce the risk of seeding and subsequent tumor progression through the chest wall at the site of biopsy. A randomized trial of 40 patients demonstrated significant benefit with no tumor progression through the port site in the treatment group receiving 21 Gy in 3 fractions administered within 10–15 days after the biopsy compared to a rate of 40% of tumor progression at the port site in the control group (9). A large randomized trial, recently published, questioned the overall benefit of prophylactic radiation after surgical biopsy (10). However, the potential benefit of prophylactic radiation approached significance when the specific subgroup of patients with epithelial mesothelioma was analyzed. Among 143 patients with epithelial mesothelioma included for randomization, port site metastasis decreased from 21% in the control group to 8% in the prophylactic radiation group treated with 21 Gy in 3 fractions with a P value of 0.057 (10). These data corroborate other studies demonstrating the greater benefit of radiation in epithelial mesothelioma compared to non-epithelial mesothelioma, possibly related to more radioresistance due to enhanced repair of DNA damage in sarcomatoid mesothelioma (11,12).

Hemithoracic radiation targeting the whole ipsilateral pleura was started in the 1970s. The groups in Helsinki and Memorial Sloan Kettering Cancer Centre in New York reported large series of patients treated with incremental doses of normofractionated radiation to the hemithorax using 3D conformal radiotherapy and observed high rates of local progression with prohibitive rate of pneumonitis of the irradiated lung (13,14). Hence, following this experience, hemithoracic radiation was predominantly performed in the adjuvant setting after extrapleural pneumonectomy (EPP) to avoid the risk of pneumonitis of the underlying lung. This bimodal approach became popular after the publication of a phase II trial by Rusch and colleagues in 2001 (15). This trial demonstrated excellent local control in patients who completed hemithoracic radiation to 54 Gy in 30 fractions after EPP with an ipsilateral pleural recurrence rate of less than 15%. Other groups have confirmed the excellent local control with high dose hemithoracic radiation regimen after EPP (16,17). Unfortunately, distant recurrence outside of the radiation field in the contralateral chest or in the abdomen was common, potentially limiting the survival benefit with this approach. The addition of chemotherapy in the induction setting before EPP and hemithoracic radiation did not appear to provide significant additional benefit and the administration of a third therapy was often poorly tolerated (18). A randomized trial assessed the benefit of adjuvant normofractionated hemithoracic radiation with a total dose of about 56 Gy after chemotherapy and EPP (SAKK 17/04). The trial was negative (19). However, the small number of patients in each arm, and the lack of standardized radiation planning and techniques limited the power of this trial.

Following the disappointing results of induction chemotherapy followed by EPP and hemithoracic radiation, most centers have switched their surgical approach to PD to facilitate postoperative recovery. PD is generally combined with chemotherapy in the induction or adjuvant setting without radiation due to risk of radiation pneumonitis. The development of modern radiation techniques such as intensity modulated radiation therapy (IMRT), however, has allowed for the safe and efficient delivery of high dose radiation to large volumes which have been explored by some centers in the induction or adjuvant setting in combination with EPP or PD (1).

The group from Memorial Sloan Kettering Cancer Centre led the development of pleural IMRT after PD for mesothelioma (20). They conducted a single arm phase II trial in collaboration with MD Anderson Cancer Centre in Texas demonstrating the feasibility to deliver 50.4 Gy in 28 fractions with the lung in place (21). The rate of radiation pneumonitis was manageable with 22.2% grade 2 pneumonitis and 7.4% grade 3 pneumonitis. No grade 4 or 5 pneumonitis was observed. Local progression occurred in 59% of the patients, mostly at sites of preexisting disease. However, after macroscopic complete resection, failure typically occurred in new sites of disease along with distant progression. The median survival was 23.7 months from diagnosis. A multicenter trial is currently ongoing in the United States to evaluate the benefit of this approach.

The article published in Cancer Radiotherapy by Parisi and colleagues went one-step further and demonstrated the safety of hypofractionated hemithoracic radiation after PD in MPM using 25 Gy in 5 fractions (2). Hypofractionated rather than normofractionated radiation has been used in the adjuvant setting (for instance after surgery for breast cancer) to improve quality of life at less cost since a biologically equivalent dose of radiation can be reached in a shorter period of time (22). In the retrospective study from Parisi and colleagues, the rate of grade 1 pneumonitis was 97% in the acute phase and 47% in the late phase after

radiation (2). There was no grade 2 toxicity and the rate of grade 3 pneumonitis was 3% in the acute phase and 6% in the chronic phase. No grade 4 or 5 toxicity was observed. Noteworthy, the radiation field was limited to the pleura at the periphery of the lung and the fissures were thus not included in the radiation field to limit the amount of radiation delivered to the underlying lung.-The median survival was 21.6 months from the time of diagnosis and the rate of local progression was about 50%.

Non-ablative hypofractionated hemithoracic IMRT started to be used in MPM by our group at Princess Margaret Cancer Centre in Toronto in 2008 in the induction setting followed by EPP as part of the prospective trial of Surgery for Mesothelioma After Radiation Therapy (3). The accelerated delivery of radiation in the hypofractionated form could be safely delivered over a short period of time, allowing the pneumonectomy to be performed within a week after radiation before the onset of pneumonitis. This approach was associated with encouraging outcome in epithelial MPM with an overall median survival of 36 months (2). The rate of ipsilateral pleural recurrence was similar to previous experiences with adjuvant normofractionated hemithoracic radiation after EPP at about 13% in the preoperative hypofractionated setting (23).

The accelerated hypofractionated dose of 25–30 Gy in 5 fractions used by our group was adapted from clinical trials in colorectal cancer (3). This dose regimen, however, is non-ablative and not expected to control macroscopic disease. Induction radiation combined with radical surgery are both required to achieve cure in colorectal surgery with this protocol. The hypofractionated regimen of 25 Gy in 5 fractions is radiobiologically equivalent to a normofractionated dose of 45 Gy in 25 fractions, which is a typical dose for induction radiation in the surgical setting for microscopic disease.

Animal experiments on ablative radiation have shown that the benefit of hypofractionated radiation is to a large part related to the development of a specific activation of the immune system against the tumor (24). Normofractionated radiation, in contrast, works predominantly by inducing DNA damage and cell senescence through the generation of oxygen reactive species. While the effect of radiation on tumor cell toxicity exhibits a monotonic dose-response relationship with increasing cell death as a function of increasing doses of radiation, the effect of hypofractionated radiation on the immune system is not. The impact of hypofractionated on the immune system can be variable depending on the tumor stroma and immunological microenvironment. Since hypofractionated radiation showed a synergistic effect with immunomodulation therapy, clinical trials combining ablative radiation with immune checkpoint inhibitors have been started in a number of malignancies.

Our group demonstrated that non-ablative hypofractionated radiation can also have a major impact on the immune system in mesothelioma (4,25). The delivery of 15 Gy in 3 fractions led to the upregulation of T cells in the tumor with specific activation of cytotoxic CD8+ T cells against the tumor and an *in situ* vaccination mediated predominantly by CD4+ T cells (4). The upregulation of regulatory T cells in the tumor, however, is immunosuppressive and may be an important limitation of hypofractionated radiation that can be reversed by preferentially targeting these regulatory T cells during non-ablative radiation (25). Hence, the combination of non-ablative hypofractionated radiation with targeted immunotherapy is a promising strategy for the near future in mesothelioma. Questions that remain open include the optimal volume and dose fractionation of radiation, the best immunotherapy agent for mesothelioma, and the timing and sequencing of all the different treatment modalities (including radiation, radical surgery, immunotherapy and chemotherapy).

In conclusion, the optimal dose and delivery of hemithoracic radiation in the treatment of mesothelioma is currently being refined and moving from normofractionated to hypofractionated hemithoracic radiation could represent an important step forward. Hypofractionated hemithoracic radiation is not yet a standard of care in mesothelioma, but better understanding of its impact on the immune system will open the door for new exciting therapy in mesothelioma with immune therapy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: de Perrot M, Cho J. Non-ablative hypofractionated hemithoracic radiation—a new standard of care in mesothelioma? J Thorac Dis 2018;10(Suppl 33):S4088-S4092. doi: 10.21037/jtd.2018.09.131

