

The rationale for neoadjuvant radiation therapy in malignant pleural mesothelioma: how smart is SMART?

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Malignant pleural mesothelioma (MPM) is a rare, aggressive tumour involving the pleura commonly associated with prior asbestos exposure. At present, there is still ongoing debate and controversy regarding its optimal management. In particular, there is no agreed upon consensus as to the most appropriate surgical procedure in this disease with various camps championing extra-pleural pneumonectomy (EPP) on one side and extensive pleurectomy-decortication (EPD) on the other.

The evidence is conflicted. The MARS Trial did not show any survival advantage using EPP (and, in fact, a possible survival disadvantage) (1). However, another publication showed significantly better local control with EPP and adjuvant radiotherapy (RT) (2). We are currently enrolling patients on our SMART (Surgery for Mesothelioma after Radiation Therapy) clinical trial where MPM patients are treated first with accelerated neoadjuvant hemithoracic RT and then followed by EPP (3). The rationale for neoadjuvant RT is provided and discussed below.

The three main pillars of oncologic therapeutics are: surgery, radiotherapy and chemotherapy. The mechanism of action for radiotherapy and chemotherapy are stochastic in nature such that their outcomes are probabilistic. The results depend, in part, on the number of tumour clonogens (i.e., tumour volume) and their biological sensitivity. Resistance to radiotherapy and chemotherapy can develop, particularly with multiple serial therapeutic challenges, due to a Darwinian culling process. This gives rise to the well-known phenomenon of therapeutic resistance.

Surgery, despite being the oldest of the three therapeutic modalities, remains the mainstay of curative, ablative therapy. Resected tumours physically removed from the

patient are certain never to recur so its treatment efficacy is very high. Unlike radiotherapy or chemotherapy, tumours do not develop resistance to surgery as this is a physical procedure (rather than a biological effect). The adequacy of surgery depends on the degree of clearance of tumour clonogens, both macroscopic and microscopic. Generally speaking, all visible (macroscopic) disease will be removed at the time of surgery (i.e., gross total resection). Therefore, when cancers recur following surgical resection, it is primarily due to the inadequacy (rather than the inefficacy) of resection, mainly as residual microscopic involvement.

The success of surgery also depends on biological behaviour of the tumour. Mathematical spatiotemporal modeling of tumour kinetics provides a useful perspective in which to view cancer growth. These use proliferative growth rates and dispersive invasion rates, based on conservation-diffusion dynamics, as the main component factors to describe tumour growth (4). Tumours with low invasive potential (such as, by definition, *in situ* tumours) are completely controlled with surgery alone and, thus, no adjuvant therapy needed. Tumours with high invasive potential (such as small cell lung cancer) are normally not cured with surgery alone. Adjuvant therapy is routinely offered, either as regional (i.e., radiotherapy) and/or systemic (i.e., chemotherapy) treatment.

Cancers, by definition, are malignant tumours capable of invading through their basement membrane and thus have the potential to metastasize and spread (in a discontinuous manner) beyond the macroscopic extent of disease. The extent of invisible (microscopic) occult disease often cannot be known with certainty. Instead, the risk is inferred from known clinical predictors for local recurrence (subject to the lens of clinical judgment), such as surgical margin status,

histopathological grade, clinical and pathological stage, and nodal status.

If recurrence risk is high, adjuvant therapy aimed at sterilizing any residual microscopic disease and, thus, reducing the risk of local recurrence, is given. Generally speaking, adjuvant therapy is given post-operatively since surgery was and still is the definitive (ablative) therapy of choice. This had the advantage of tailoring treatment to smaller subset of patients deemed at sufficiently high enough risk to warrant adjuvant therapy and justify the added toxicities.

MPM patients commonly present with a malignant pleural effusion so the entire pleural space, including the lobar fissures, are potentially at risk for microscopic involvement. It is, therefore, not surprising that EPP alone often gives rise to a positive resection margin (R+ resection) and local failure. Adjuvant RT has been shown to be effective at reducing the risk of local recurrence in the hemithorax (2,5).

The success of adjuvant therapy leads naturally to consider expanding the indications for adjuvant therapy in MPM patients to more advanced disease. More advanced disease is generally more challenging to resect. One successful strategy tried is clinical down-staging through neoadjuvant chemotherapy. Trimodality therapy, where chemotherapy is followed by EPP and adjuvant hemithoracic RT, was introduced in order to improve resectability of difficult tumours and to improve tumour control (6,7). A major disadvantage is that some patients will not respond to chemotherapy and, thus, will not proceed to EPP. Trimodality therapy is associated with high attrition rates where only half of original patients actually complete all three modalities, often due to disease progression (8).

The risk of disease progression can be minimized by shortening the time interval between diagnosis and EPP as well as using a more efficacious agent against MPM. Neoadjuvant chemotherapy has a response rate of approximately 30–40% which implies that most patients are non-responders and, thus, can progress during this time. An alternative neoadjuvant approach is shorted accelerated hypofractionated RT where the treatment is delivered in a truncated amount of time (i.e., 1 week) before the tumour has an opportunity to progress. In the Swedish Rectal Study, rectal cancer patients received neoadjuvant RT consisting of 25 Gy in 5 fractions over 1 week followed by total mesorectal excision (9). This resulted in improved local control and increased overall survival. The main mechanism of action is presumably the sterilization of residual

microscopic disease, potentially present post-operatively.

Aside from the potential benefits of clinical down-staging of macroscopic disease and the sterilization of microscopic boundary of disease, neoadjuvant therapy may also play a role reducing the risk of distant failure in MPM. It was observed that many of these patients developed distant disease, usually involving the contralateral lung and/or peritoneal cavity. We hypothesized that some distant failures were due to incidental tumour spillage during EPP into these areas.

This suggests that distant failure rates can be improved by reducing the number and proliferative capacity of tumour clonogens that spill outside the involved thoracic cavity. The SMART study was designed to test this hypothesis. Resectable MPM patients received 25–30 Gy in 5 fractions over 1 week to the hemithorax followed by EPP the following week. These patients must proceed to pneumonectomy after RT due to expected severe (fatal) radiation pneumonitis. The overall treatment time was shortened (less than 2 weeks) to allow the lung to be resected before any significant pneumonitis develops. Our initial experience has been encouraging (3,10). Epithelioid MPM patients undergoing SMART protocol had excellent 3-year overall survival of 70–80%.

Although we will have to await completion of the study and its follow-up before being able to make any firm conclusions, the outcomes seen in the SMART study are, so far, consistent with the hypothesis of incidental spillage of microscopic MPM clonogens outside the thoracic cavity at the time of EPP. It has the added benefit of high treatment tolerability where every patient successfully completed the planned therapy of RT followed by EPP. However, this is at the cost of significantly increased treatment complexity, requiring high degree of coordination and cooperation between the radiation oncologist and the thoracic surgeon.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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