Secondary malignancy after radiotherapy for Hodgkin Lymphoma

Hodgkin lymphoma (HL), formerly called Hodgkin disease, has attained high survival rates (≥75% at ten years for all grades and stages combined, age-standardised), with continued improvements in treatment modalities since the 1940s, when radiotherapy was first used to combat the disease. Today, sequential chemotherapy and radiation are used in many cases, but certain groups of patients, dependent on stage and prognostic factors, will have either chemotherapy or, in limited stage nodular lymphocyte predominant HL, radiotherapy alone to minimise exposure to potentially toxic treatment which carries the risk of long-term sequelae, such as the recognised increased risk of secondary cancers in HL survivors.

The original radiotherapy approach for limited (stage I or II) disease above the diaphragm is known as wide-field (WFRT) or mantle radiotherapy, a mantle being a cloak worn draped over the shoulders, and the distribution of radiotherapy fields resembles this appearance. This approach treats the major lymph node groups above the diaphragm, including mediastinal, hilar, axillary, supraclavicular and cervical chains. The standard dose would be considered as 30-35Gy in 20 fractions over three weeks. Although this article focuses mainly on the after-effects of WFRT to the upper body, a similar approach for disease below the diaphragm is termed inverted-Y radiotherapy, treating the para-aortic, iliac and pelvic nodal groups. A combination of wide-field upper body and para-aortic nodal radiotherapy is referred to as extended-field radiotherapy (EFRT).

Immediate toxicities of WFRT include reddening of the skin, hair loss in the treated area, oesophagitis, nausea, fatigue and bone marrow suppression. These would be generally managed with supportive medications and blood products as required. Radiation pneumonitis (RP) can develop in those treated with mediastinal radiotherapy, which causes cough and pronounced breathlessness in up to 15% of treated patients and is managed with steroids. Radiologic studies showing signs of inflammation in the affected lung tissue indicate the numbers affected by subclinical RP is much higher – around 65% in some series.

Long-term side effects of WFRT, among others, include soft tissue fibrosis and skin thickening, telangiectasia, hypothyroidism, cardiac perfusion defects and reduction in ejection fraction and the development of a second solid tumour.

Lung fibrosis can develop in the months and years following RP. The affected areas often demonstrate straight edges on imaging and sharp opposition to unaffected tissue, corresponding to the applied radiation fields at treatment. Certain groups of patients are at greater risk of developing fibrosis: Older age at treatment, those with co-morbidities and sequential chemotherapy delivery.

Increased risk of secondary solid tumours

Secondary solid tumours most commonly develop in the regions of the body within the radiation field during therapy. Generally, there is a long latency period prior to presentation of these tumours from around five years to greater than 25 years after diagnosis of HL.

The most common solid tumour overall post-WFRT in treated HL is lung cancer, with an increase in relative risk of between two to five fold when all ages at diagnosis of HL and both sexes are considered. Smoking either before, during or after treatment increases the risk 20 fold. The risk of developing a secondary lung cancer rises with increasing age at diagnosis of HL, with a peak around the 51-60 age group. It is important to note that chemotherapy for HL can elevate lung cancer risk (up to six fold above expected) but combined treatment with chemotherapy and radiotherapy raises the risk further, particularly when alkylating agents such as procarbazine and mechlorethamine (given in the MOPP regimen) are used, with an eight fold increase in lung cancers, rising to 13 fold when nine or more cycles of these agents are delivered. The most commonly used HL chemotherapy regimen, ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) does not appear to increase lung cancer risk above expected rates. Unfortunately, many lung cancers present late, at stage 3 or 4, and the survival of radiation induced lung cancer is generally poor, with a median survival of four months. If the cancer is discovered incidentally the outcome is slightly better. We were prompted to write this review after several secondary tumour cases passed through our lung cancer multidisciplinary meeting within only a few months. Although this piece of work is by no means an exhaustive breakdown of increased risks of HL therapy in the longer term, we wished it to serve as a reminder that the described increase in risk translates to relevance in today’s clinical practice for this patient group.

In females, the most common second cancer post WFRT is breast cancer, which is increased three to five fold, with the risk being highest in those who were under the age if 30 at the time of treatment, and especially those under the age of 18 with a relative risk increase up to 20 fold. Unfortunately, one in six women who survive a secondary breast cancer will go on to develop a third cancer within 10 years, with 64% of these subsequent malignancies manifesting as further breast cancers.

An excess of other cancers is observed in HL patients who were treated with WFRT. Although the absolute numbers of cases are smaller, the relative increase in risk of some cancers is greater than for more common secondary tumours such as lung or breast. Oesophageal and thyroid tumours can be increased by around two to 20 fold, the incidence rising with time since treatment. Stomach cancers are also found more often than would be otherwise expected (1.4 to 5.4 fold), but less so than oesophageal or thyroid malig-
nancy. This may reflect the fact that stomach tissue, given its anatomical location, received a lesser radiation dose in supra-diaphragmatic WFRT (up to 13Gy) compared to those mediastinal and neck tissues that were exposed to the entire treatment dose of 35Gy.2

Non-Hodgkin lymphoma, bone and connective tissue sarcoma rates are increased (three to eight fold), but perhaps the most striking increase of the rarer secondary tumours is in cases of acute non-lymphocytic leukaemia (three to five fold).

Those patients who underwent inverted-Y WFRT have, as might be expected in light of the mantle WFRT data; increased rates of colorectal (three to five fold), cervical (up to five fold) and bladder cancers (up to six fold) in addition to sarcomas and haematologic malignancies as described above.2

Once these elevated risks became apparent, as long-term survival and follow-up data was gathered and analysed for HL patients, efforts were made to reduce the area treated and dose applied to minimise risk while still providing long-term control of the HL.

Current clinical practice delivers radiotherapy for limited stage HL in lower doses (20Gy vs 30-35Gy), and only to the nodal chains affected by HL (known as involved-field radiation, IFRT). Further adaptation of the method is to treat only the nodes directly involved with disease – involved-node radiation, INRT. These changes seem to have helped lower the cancer risks after treatment; but given the latency period for development of secondary tumours, this information is still being pooled for newer techniques and is not always reflective of the initial treatment, as chemotherapy or subsequent salvage therapy may not be accounted or adequately adjusted for, until sufficient patients are treated and followed up. Predictive modelling of relative risk between WFRT (35Gy) and IFRT (35Gy) demonstrates a reduction of 64% in female breast cancers and 35% in male lung cancers simply by reducing the excess volume of tissue within the radiotherapy field. Moving to 20Gy IFRT appears to reduce the risk by a further 40%6,7,8 without an appreciable increase in treatment failure.9 This would appear to justify the approach of treating the smallest area possible to effectively treat the HL but without encompassing unnecessary sites to minimise toxicity and late effects. Further analysis and prospective trials are warranted, to provide data which will assist in selection of treatment modalities and the counselling of patients undergoing HL therapy. In the meantime, we will continue to see secondary tumours due to WFRT in previously treated HL patients. It is vital we are clinically aware of the potential for these unwanted “off-target” effects, in order to attempt to secure earlier diagnosis of secondary cancers, and ultimately aim for better outcomes in this setting.

Acknowledgements

We would like to thank Professor Peter Hoskin (Mount Vernon Cancer Centre) for reading the manuscript and providing constructive criticism; and Megan Cope (Clinical Photography and Illustration, East and North Hertfordshire NHS Trust) for production of the mantle radiotherapy diagram.

References

Figure 1
Mantle radiotherapy fields.

Figure 2A
Post treatment radiotherapy changes in the lung apices with well defined margins consistent with the radiotherapy treatment field.

Figure 2B
Defined soft tissue mass in the right upper lobe.

Figure 2C
The defined soft tissue mass in the right upper lobe shows significant PET avidity consistent with a primary lung tumour.