New radiotherapeutic approaches for improving cure and palliation of lung tumors
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Summary

Although advances in diagnostic and therapeutic options have led to a better survival in cancer patients, there remain several challenges that need to be addressed, particularly in patients with lung cancer.

In patients treated for lung cancer, survival can be influenced by recurrent disease or a second primary tumor. Following a curative treatment for lung cancer, survivors have a 3-6% risk per person year of developing a second primary lung cancer (SPLC). Consequently, several guidelines now recommend the use of CT surveillance.

Chapter 2 describes outcomes of 107 lung cancer survivors, who were diagnosed with early stage SPLC and were treated with stereotactic radiotherapy (SABR). Our analysis showed a three years overall survival (OS) (60%) and local control rate (89%), that are comparable to the outcomes for a first lung cancer. Toxicity was uncommon, despite the fact that 73% of patients had undergone a prior (bi)lobectomy. Given these promising results after SABR for SPLC, CT surveillance seems appropriate in patients who may be unfit, or unwilling, to undergo surgery after curative treatment for an initial lung cancer.

Because of a shared etiology of tobacco exposure, patients with squamous cell head and neck carcinomas (HNSCC) are also at risk of developing a SPLC. Population-based studies show that patients with SPLC after HNSCC have a poorer prognosis compared to patients with a primary lung cancer. In chapter 3, we describe outcomes in patients with HNSCC and SPLC treated at our institution. Of a 181 patients identified, 40 patients had a synchronous HNSCC - SPLC and 141 presented with metachronous HNSCC-SPLC. In this cohort, the survival of patients who were diagnosed with advanced disease was indeed poor; 11.0 and 4.6 months for locally advanced and metastatic disease, respectively. However, patients who were diagnosed with early stage SPLC had a significantly better survival, with a median OS of 95.4 months. CT surveillance strategies in HNSCC patients may positively influence survival, and this warrants further investigation.

If a disease recurrence or new primary lung tumor develops in a previously treated area following high-dose radiotherapy, treatment options, such as a
salvage resection or reirradiation are often considered to be limited. This is mainly due to concerns about toxicity. The availability of improved radiotherapy techniques, however, has increased options for reirradiation. In chapter 4, we describe our experience with 24 patients treated with high-dose conventional thoracic reirradiation. The majority of patients (63%) had stage III non-small cell lung carcinoma (NSCLC) at both initial and second treatment. Median OS after reirradiation was 13.5 months, with a 1-year survival of 51%. Three patients died with possible grade 5 toxicity (bleeding). Planning target volume (PTV) at reirradiation was the most important prognostic factor, in which a smaller volume (PTV <300cc) was associated with a significantly better survival. The magnitude of overlap between the initial and subsequent PTVs, and between dose distributions, did not appear to influence survival. Further studies are needed to confirm feasibility and prognostic factors, and to establish reliable normal tissue tolerance doses for reirradiation.

As diagnostic imaging continues to improve, the number of lung cancer patients diagnosed with multiple primary lung cancers (MPLC) is increasing. Current guidelines recommend a curative approach when early-stage MPLC is diagnosed, based on favorable outcomes have been reported after surgery. In chapter 5, we describe outcomes following stereotactic ablative radiotherapy (SABR) in 62 patients with MPLC. In our series, the median OS was 31 months, with an actuarial 2-year survival of 56%. No grade 4 or 5 post-SABR toxicity was observed. Two-year local and regional control rates were 84% and 87%, respectively. As toxicity is limited, we believe that SABR should be considered when patients with lung cancer present with a synchronous second lesion, and where no nodal involvement is detected.

In contrast to early-stage lung cancer, survival in most patients with metastatic lung cancer is poor. However, it has been suggested that there might be a subgroup of patients, in whom the number of metastases is limited ('oligometastases'), who have a favorable prognosis, if all lesions can be treated with radical intent. Chapter 6 describes outcomes of 61 lung cancer patients who, at the time of diagnosis, already had 1-3 metastases. These patients were treated with radical intent to all sites of disease. The 1- and 2-year OS in this cohort were 54% and 38%, respectively. These favorable outcomes were associated with the intra-thoracic disease status: patients with small
radiotherapy treatment volumes or resected disease had the best OS. In addition to evaluating outcomes of lung cancer patients with synchronous oligometastases, we also reviewed the literature on the use of radiotherapy for oligometastases in chapter 7.

Finally, improved technology for reconstructing previous doses can permit safer thoracic reirradiation. This reconstruction of the previously administered dose can be rendered difficult due to anatomic changes by tissue loss or post-irradiation fibrosis. A technique to account for anatomical changes and more accurately reconstruct prior doses, is deformable image registration (DIR). In chapter 8 we compare the performance of DIR to rigid image registration (RIR), to evaluate accuracy.

In a palliative setting, radiation treatment often consists of just a single fraction. As a palliative radiation dose, is relatively low, the sparing of organs is often not given a high priority, and a simple technique is use, so time can be spared, and patients can be treated quickly. However, despite the low dose, it can be associated with toxicity. Furthermore, with the increased use of targeted agents, organ sparing radiotherapy might become more important, as awareness of the potential for radiation-drug interactions increases. In chapter 9, we describe the use of intensity modulated radiotherapy (IMRT) for large-field palliative pelvic bone treatments, which can substantially reduce the dose delivered to abdominal/pelvic organs, and show that it is possible to introduce such techniques into routine care.