Chapter 10

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An improved understanding of the epidemiological aspects and molecular characteristics of lung cancer has led to new challenges, while the breakthroughs in molecular targeted therapies have led to new dilemmas in our daily practice. The work performed for this thesis attempts to address some of these issues.

Managing Survivorship

Even after curative treatment, lung cancer patients are faced with the risk of disease recurrence and developing new a primary lung cancer. In 1294 patients who underwent a resection for an early stage lung cancer, followed by a CT-scan of the thorax at least every 6-12 months, the risk of disease recurrence was 6-10% per person-year during the first four years, and decreased thereafter to 2% ¹. Moreover, the risk of developing a second primary was 3-6% per person-year and did not decrease over time ¹. The persistently high risk of death in lung cancer patients is illustrated by survival data from the SEER database on 31,026 patients who were still alive at least 5 years after being diagnosed with NSCLC ². This study revealed that both overall survival and disease specific survival keep diminishing, even after more than 15 years (Figure 1.).

Figure 1. Graphs of DSS (top red line) and OS (bottom black line) in patients with NSCLC surviving more than 5 years. CL, Confidence limit; DSS, disease-specific survival; OS, overall survival. Derived from ².
A similar situation is encountered in patients with head and neck cancer, where the risk of second primary lung cancers (SPLC) after 5, 10, and 15 years post-treatment is 6%, 11%, and 16%, respectively (Figure 2). 

![Figure 2. Kaplan–Meier risk of developing lung cancer after head and neck cancer among 61,883 patients. Derived from 4.](image)

Our study on treatment outcomes for SPLC after HNSCC (Chapter 3), found a better prognosis if SPLC was diagnosed in an early stage. Unfortunately, more than half of the SPLC after HNSCC were found at a more advanced stage, presumably due to a lack of comprehensive surveillance.

The National Lung Screening Trial (NLST) compared the use of a low-dose CT-scan versus a chest radiograph to screen for lung cancer in high-risk patients, and showed a relative reduction in mortality from lung cancer of 20% with CT screening. Given the high 5-year incidence rates of SPLC in the two patient populations studied above, and the far lower risk of developing a lung cancer in populations undergoing CT screening, low-dose CT in lung and head and neck cancer survivors deserves attention. An absolute risk-prediction model for lung-cancer mortality in the NLST’s chest radiography group has been developed, which revealed the following quintiles for the 5-year risk of
lung-cancer death: 0.15 to 0.55% in quintile 1 (lowest risk) to more than 2.00% in quintile 5 (highest risk). Consequently, the number of participants who would need to be screened to prevent one lung-cancer death decreased from 5276 among the 20% of participants at lowest risk to 161 among the 20% of those at highest risk. Similarly, the number of stage I lung cancers increased significantly with an increasing risk of lung-cancer death (40 in quintile 1 vs. 215 in quintile 5, \( P<0.001 \) for trend). In the light of available data suggesting that the 5-year risk of SPLC exceeds 6% in survivors of both lung and H&N cancer, we would argue that secondary CT screening in these groups is justified 7,8.

Distinguishing SPLC from metastasis continues to pose a challenge. Besides using array comparative genomic hybridization (arrayCGH), the use of genomic rearrangements from mate-pair sequencing demonstrates promise in distinguishing if two lesions are related (primary-metastasis) or unrelated (two different primary tumors) 9. However, to distinguish two lesions based on tissue samples, means that a biopsy is needed. Currently, it is not feasible to retrieve a tissue sample in every patient (Chapter 1), as a biopsy can pose risks, especially to patients with significantly impaired lung function 10. Less invasive approaches for obtaining tissue samples are required, but if the distinction cannot be made, the decision made by a multidisciplinary tumor board should take precedence, and patients should be given the benefit of the doubt, which usually means managing them as though they have 2 separate primary tumors.

After conventional radiotherapy, and to a lesser extent, SABR, local and regional recurrences, still pose a challenging clinical problem. In patients without widespread metastases, an attempt to perform curative treatment for lesions located in a previously irradiated area appears to be reasonable. Three clinical scenarios may be encountered by radiation oncologists in clinical practice, although published data is limited:

- Stereotactic radiotherapy (SABR) followed by repeat SABR in the same area
- High-dose (chemo) radiation, followed by SABR
- Conventional (chemo) radiation followed by re-treatment with conventional radiation

In practice, re-irradiation for recurrent disease remains a challenge due to the absence of reliable data on normal organ tolerance doses in this setting. More
accurate tools that can provide data on the accumulation of doses from both courses of radiation are entering clinical use, but the problems arising due to loss of tissue and fibrosis in previously irradiated areas may limit the clinical conclusions that can be drawn from such data. In the first scenario (SABR after SABR), high rates of toxicity have been reported when repeat SABR is performed in patients with central lung tumors. A recent review also suggests that using SABR for re-irradiation after previous conventional radiotherapy was associated with higher toxicity for central tumors. However, the available studies comprised a very heterogeneous, and selected, patient population, receiving a range of treatment regimes, with short follow-up. We explored the third scenario (conventional after conventional), and found that the acute toxicity of re-irradiation appears to be acceptable when modern radiotherapy techniques are used. Once again, central re-irradiation may be associated with higher risks and the prognosis for patients requiring large treatment volumes was worse. In-field tumor recurrences after re-irradiation remain a major problem, and the median survival in our selected patient population was only 13.5 months. Consequently, the level of evidence for a beneficial effect for high-dose re-irradiation in all three scenarios remains low, especially for lesions located centrally close to the hilar structures. Nonetheless with about 25% of patients surviving 2 years, we believe that its use is justifiable in carefully selected patients and after appropriate discussion of risks and potential benefits.

**Extending limits for radical treatment: multiple primary tumors and oligometastases**

Patients who present with multiple primary lung cancers (MPLC) represent an under appreciated, but clinically relevant problem, as highlighted by incidences of 5 and 9% in two recent screening studies. Similarly, rates of MPLC were respectively 7 and 12%, following video-assisted thoracoscopic surgery (VATS) and thoracotomy in early stage lung cancer. Our results revealed good local control and survival using SABR in patients presenting with MPLC (Chapter 5), findings confirmed recently by the results from the MD Anderson Cancer center. An interesting observation in our study was the higher incidence of regional lymph node recurrences in patients presenting with two synchronous ipsilateral lesions. This finding suggests that minimally invasive endobronchial and esophageal endosonography (EBUS and EUS) may be indicated as a
staging procedure for this group of patients. The prospective evaluation of EUS-EBUS in addition to PET-CT scan before SABR, is the subject of our recent multicenter, prospective, diagnostic single-arm study called **ST**ereotactic A**blative** radiotherapy for lung cancer after sta**G**ing with E**ndosonography (STAGE; NL46486.018.13). A similar trial in Canada also aims to compare the results after nodal staging with EBUS-TNA with the findings on CT and FDG-PET scans taken prior to the EBUS-procedure (NCT01786590).

The treatment of so-called oligometastases is still a controversial topic (Chapter 6 and 7). Although the idea of the existence of oligometastases can be very appealing to both physicians and patients, there is only limited data in support of this theory. In patients with lung cancer, an individual patient data meta-analysis was published recently. Using the data of 757 patients with oligometastatic lung cancer, this study identified three risk groups 17, which can guide us in our decision on how to treat patients with oligometastases. The group with the best survival (‘low-risk’) had a 5 year overall survival of almost 50%, and was formed by patients with metachronous oligometasases (> 6 months). The ‘intermediate risk’ group was formed by patients with lung cancer and synchronous oligometastases, without evidence of nodal disease (N0), and had a 5 year overall survival of 36%. The group with the worst survival (‘high risk’), was formed by patients with lung cancer, synchronous oligometastases and evidence of nodal disease. Their 5 year overall survival was only 14%.

**Figure 3.** Flow-chart of the Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastastic Tumors (SABR-COMET): a randomized phase II trial.
Available data based on observational studies, or highly selected patient groups, that report better-than-expected outcomes cannot exclude the possibility of patients having more indolent disease\textsuperscript{18}. Our ongoing multicenter, randomized phase II trial (NCT01446744; Figure 3)\textsuperscript{19} will hopefully be a stepping stone towards a phase III trial for treating oligometastases, and provide higher quality data.

**Reducing treatment toxicity using advances in technology**

Following thoracic irradiation, changes in lung tissue, such as atelectasis and fibrosis, can become apparent\textsuperscript{20, 21}. In addition, factors such as changes in body weight and differences in positioning on consecutive CT-scans. All these changes can make it difficult to reconstruct the doses received by specific anatomical regions in patients who present for thoracic re-irradiation. In some cases, deformable image registration may help to account for these changes and assist the planning of re-irradiation. However, validating the accuracy of DIR is a challenge. Our research (Chapter 8) showed that DIR can better account for anatomical differences than when using a rigid registration, but the technique is not without limitations. This point was illustrated when DIR was evaluated in a more favorable setting, in a study validating several DIR-algorithms using a thoracic 4D-CT-scan in which 300 anatomical landmarks were identified on both the inspiration and expiration phase of this scan\textsuperscript{22}. The study showed that DIR performed reasonably well for small displacements, but that its accuracy quickly deteriorated when the displacement of landmarks between the two scans increased. Due to the inability to directly verify the registration, for now, DIR should be used with caution, especially when gross anatomical changes have occurred.

Improved technology for radiotherapy delivery has mainly been used for curative treatments, with an apparent reluctance to do so in a palliative setting. In part, this may be due to the perceived time and effort required to perform such treatments. However, acceptance can be facilitated when techniques can be shown to result in meaningful benefits to patients. A good example of the former in a palliative setting, is illustrated by the use of stereotactic radiosurgery (SRS) for brain metastases, for which there is level I evidence for benefit\textsuperscript{23}. Due to concerns about the efficacy and toxicity associated with whole-brain radiotherapy (WBRT), current Dutch guidelines recommend using SRS for 1-3 brain metastases without WBRT, as it appears to reduce the
risk of neurocognitive toxicity. We have recently extended this to selected patients with more lesions, again in an attempt to reduce the risks of toxicity encountered with irradiating the whole brain.

The work performed in this thesis (Chapter 9) also provided an example of where fast, bowel-sparing volumetric modulated arc therapy (VMAT) was implemented in the palliative setting for bone metastases. The use of conventional radiation fields for palliating painful metastases was associated with diarrhea in 28% of patients after a single dose of 8 Gy. With the growing trend of treating patients with NSCLC with targeted therapies, such as tyrosine kinase inhibitors (TKI), it becomes more important to use advanced techniques to spare organs at risk, even in a palliative setting, in order to minimize the risk of (unexpected) toxicity and to minimize treatment interruptions.

Figure 4. Subtyping Progressive disease. Abbreviations: CNS = central nervous system; PD = progressive disease. Derived from 25.

Most patients with lung cancer who present with oncogene-driven tumors acquire resistance to targeted therapies. This can manifest in different clinical scenarios: systemic progressive disease (progression at many sites),
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oligo-progressive disease (progression in the form of a single lesion or a small number of new/existing lesions) and isolated, so-called central nervous system sanctuary progression (Figure 4.) 26.

Recent guidelines have now made recommendations to address these clinical scenarios. Updated ESMO guidelines recommend that when oligometastatic progression is detected during treatment with tyrosine kinase inhibitors (TKI's), the use of a local treatment such as surgery or radiotherapy should be considered, and TKI's 'continued or resumed' 27. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend that when faced with symptomatic progression in the brain or with an isolated extra-cranial lesion, the clinician should consider local therapy and continue the TKI 28. In practice, the decision about whether to continue with the targeted agent during high-dose radiotherapy (including SABR or stereotactic radiosurgery), should be carefully considered by the treating group. In many cases, we currently elect to stop the agent around the time of radiation therapy.

The concomitant use of chemotherapeutic and/or targeted agents with radiation may, however, cause an increase in toxicity. For example, the combination of vascular endothelial growth factor (VEGF) and radiation has been linked with serious lung and gastro-intestinal toxicity, such as pulmonary fibrosis, tracheo-esophageal fistula, bowel ulceration and even perforations, which may be fatal 29,30. In addition, in patients treated with sorafenib (a kinase inhibitor) after prior radiation therapy, a recall effect of the radiation has been described, which can cause, for example, radiation dermatitis and pneumonitis 31. In such cases, we recommend that the radiotherapy techniques used should be chosen carefully, and that advanced techniques be used to spare potential organs at risk, even in relatively low-dose palliative treatments. (Chapter 9 and Figure 5).
Figure 5. The plan on the left is typical of a conventional cervical spine treatment. Two lateral fields are used to treat the target volume (red line), but they also irradiate everything inbetween (including the spinal canal and esophagus) with a dose that is similar to the prescription dose (in this case the prescribed dose was a single fraction of 8Gy and the colorwash represents a dose of at least 7.6Gy). On the right is a stereotactic radiotherapy plan for the same target volume (red line). In this case, intensity modulation is used to control the dose that is delivered to different regions and discriminate between the target and organs at risk (OAR). This results in relative sparing of the OAR (e.g. spinal cord an esophagus) and enables dose-escalation in the target (in this case the colorwash represents a dose of at least 30Gy, delivered in 5 fractions). Such techniques (with or without dose escalation may be useful in trying to reduce toxicity due to interactions between radiation and targeted therapies.

Additional directions for the future

In addition to the above challenges, two other topics are worthy of mention. It is important for healthcare professionals to encourage all patients to cease smoking, as cessation at any age dramatically reduces death rates 32. The effectiveness of systematically providing support for smoking cessation to all adult smokers admitted to the hospital, relative to usual care, is established 33. Patients should be aware that having an initial smoking-related cancer places them at risk of developing a second malignancy 34. In addition, current smokers with lung cancer have an increased risk of mortality, whereas former and never-smokers have comparable survival (Figure 6)35.
In addition, more attention must be paid to the quality of life of lung cancer survivors. A systematic review on quality of life (QoL) of lung cancer patients after a surgical resection, revealed a significant incidence of pain, fatigue, dyspnea and coughing, depressive symptoms and anxiety. It is interesting to note that studies describing QoL after SABR, report that the QoL is preserved, which is in marked contrast to the surgical literature. At present, addressing psychological symptoms that may influence QoL, is not routine in the follow-up of lung cancer patients. One model for a ‘survivorship program’ for lung cancer patients, in which patients who have been disease free for a year are transferred to a nurse practitioner-led program, has recently been described. Such an approach might help in addressing symptoms, such as depression and anxiety, more often. Together with smoking cessation programs, this might improve the lives of lung cancer patients in the future.
References


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