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Chapter

Radiotherapy: An Alternative to Surgery

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Abstract

Many major technical developments have occurred during the last decades in radiotherapy: our efficacy has improved with less toxicity. Nowadays, it allows us to challenge the role of surgery as a local modality for lung cancer both for early, advanced and even metastatic disease. In the present paper, we will mainly discuss the role of SBRT for stage I lung cancer, the place of conventional radiotherapy for stage III and we will review the current treatment of small cell lung cancer from a radiation oncologist perspective.

Keywords: SBRT, trimodality stage III, small cell lung cancer chest RT, PCI

1. Introduction

Radiation oncology is an important player in the treatment of lung cancer either alone taking advantage of the new technological developments (stereotactic radiotherapy, intensity modulated radiotherapy, image guide radiotherapy) or with surgery and systemic treatment (chemotherapy, immunotherapy, targeted drugs). To-day, radiotherapy may even challenge surgery as the loco-regional treatment both for stage I and III non-small cell lung cancer (NSCLC) and is the local treatment for small cell lung cancer (SCLC). In the present chapter, we will discuss those different clinical situations and presenting the current knowledge.

2. Stage I lung cancer: radiotherapy as an alternative to surgery

2.1 Stereotactic radiotherapy for early stage lung cancer (SBRT)

Surgery is the treatment of reference for early stage lung cancer and a lobectomy or an anatomical segmentectomy in selected cases coupled with a lymph node dissection is the preferred approach [1]. For early stages, surgery is generally technically less complex and associated with less toxicity and mortality than for more advanced stages. Still, some patients cannot undergo surgery due to medical comorbidities. In the past, conventional (long course) radiotherapy or even no treatment was often proposed to those patients; the outcome was very poor: in a review, the 2-year survival rates range from 22 to 72% and the 5-year survival rates from 0 to 42% [2].

In early 1990's, a new radiotherapy technique emerged in Europe and Japan, built on the experience with intracranial stereotactic treatments, called stereotactic

hypofractionated radiotherapy, stereotactic irradiation (STI), or extracranial stereotactic radioablation (ESR), and now more commonly referred to Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Radiotherapy (SABR) [3, 4]. This is a novel form of high-precision, image-guided radiotherapy and aims to deliver higher radiation doses in a reduced number of fractions resulting in a higher Biologically Effective Dose (BED) than "conventional RT", i.e. a higher biological impact for a given physical dose. This approach treats only the tumour without any coverage of the hilar or mediastinal lymph nodes.

Several retrospective studies observed encouraging results for early stage lung cancers and in 2006, the results of a prospective phase II trial testing SBRT for inoperable patients was published by Timmerman et al.: encouraging oncological outcomes were confirmed with 60 Gy or 66 Gy delivered in 3 fractions for T1 or T2 tumours [5–7]. However, the trial also showed an 11-fold increase in high grade toxicity, including even death. This was associated with the treatment of perihilar/centrally located tumours, those in a region close to the proximal bronchial tree that was later referred to as the "no-fly-zone".

In 2010, the phase II trial NRG Oncology Radiation Therapy Oncology Group (RTOG) 0236 reported a 97.6% 3-year local control (LC) rate (95% CI 84.3–99.7) for a cohort of 55 patients with a T1–T2N0M0 peripheral lesion (tumour diameter less than 5 cm) treated with 3 fractions of 18 Gy [8]. Toxicity was limited with 2 grade 4 events and no grade 5. This trial updated results was reported in 2018 with a median follow-up of 48 months: recurrences at the primary site were rare at 5 years (7.3%) but the 5-year disease-free survival and overall survival (OS) rates were respectively 25.5% and 40.0% [9]. If SBRT is very effective to treat a specific lesion, occult spread may already occur and impact prognosis as well as intercurrent death related to the patient comorbidity. Data from larger cohorts and many other phase 2 trials also confirmed that SBRT is an effective and safe approach for inoperable patients but some studies also included medically operable patient who had refused a surgery [10–13]. The latter group showed a better outcome due to less intercurrent death with even long term survival data close to the surgical series [14]. Furthermore, in the US National Cancer Data Base, Nanda et al. reported better survival for elderly patients (70 years or older) treated with SBRT than no treatment and this was still valid regardless of patient age [15]. Last but not least, SBRT was compared to conventional RT in two randomised trials: a better outcome was observed with less toxicity and was more convenient for the patients by reducing the travels to the radiotherapy department [16, 17].

2.2 Central tumours

Central tumours represent a challenge after the toxicity reported by the RTOG phase II trial [7]. Different groups have tried to identify treatment possibilities for these patients, mainly with different dose-fractionation schemes or with lower doses to the periphery of the planning target volume (PTV) than 3 fractions of 20 Gy [18–21]. With more data available from many centres, a distinction was necessary within the central tumours located within the no-fly-zone: the distance to the bronchial tree and the oesophagus was crucial in determining the toxicity risk and leading to the definition of ultra-central tumours (UC): meaning the PTV overlaps the proximal bronchial tree or the oesophagus [21, 22]. A systematic review published in 2019 reported on the results of nine trials with at least 5 UC tumours, for a total of 291 patients but all studies have a slightly different definition for an UC [23]. SBRT treatments delivered a BED (for a α/β ratio of 10 Gy, $BED_{10\ Gy}$) of 67.2 Gy (48 Gy in 12 fractions) to 112.5 Gy (50 Gy in 4 fractions). Grade 3 toxicity or more ranged from 0% in two smaller-sized trials up to 55.5% at 2 years including 10

deaths in a cohort of 47 patients. In this particular trial there was no dose limit to the trachea and main bronchi and there was a great difference between the prescribed dose and the maximum dose delivered. In total, 8 studies reported grade 5 complications, mostly due to haemorrhage (15 of 22 cases). All studies reporting statistical comparisons of outcomes did not find differences in OS (6 studies) or LC (4 studies) between central and ultra-central tumours. Furthermore, six trials described a statistical comparison of toxicity rates without any significant difference.

The question of the best radiation management for non-peripheral tumours is currently still open and being examined by the LungTech and SUNSET trials, respectively investigating central and ultra-central localizations [24, 25]. In current clinical practice, SBRT is commonly performed for central tumours or isolated mediastinal lymph nodes at lower doses than peripheral tumours. In Onishi experience, a $BED_{10\ Gy} > 100$ Gy was decisive to obtain a high local control and survival with SBRT [6]. For (ultra-)central tumours, this cannot always be achieved, but at the same time, dose constraints for central airways and oesophagus can be observed to avoid severe toxicity but at the price of a lower efficacy.

2.3 SBRT vs. surgery

Since the early 2010's, SBRT is accepted as a standard treatment for patients medically inoperable or refusing surgery. As comorbidities can also prevent a safe biopsy, SBRT is now accepted for the management of lesions highly suspicious of lung cancer without necessary a histological confirmation. SBRT has a favourable toxicity profile and a good local efficacy and SBRT may challenge surgery. Survival outcomes of SBRT could seem somewhat poor when compared to surgical series. However, most patients treated with SBRT present severe comorbidities or were older and such a direct comparison of survival is not appropriate. These comorbidities could dramatically impact prognosis by influencing further treatments, non-cancer related survival...

Several studies performed propensity score matching to compare surgical and SBRT patients' outcomes with controversial results. A meta-analysis of propensity score matched studies was published in 2019 including 15 studies [26]. The results seemed to confirm a better 3-year OS after surgery but these results were questionable as unbalance remained in the matchings, meaning that patients were not similar after all. When restricting the analyses to studies with comparable covariates, no statistically significant difference in OS was found anymore. Selection biases seem inevitable in clinical practice, and so the need for randomised trials is generally recognised.

Several phase III trials randomised patients for SBRT or surgery and were initiated by different groups. STARS (registered as NCT00840749 on ClinicalTrials.gov), started in 2008 in the United States, aiming to identify a difference in 3-year OS, which required enrolment of 1030 patients over an expected period of 7 years. After having recruited 36 patients in 4 years, enrolment was prematurely closed. The ROSEL trial (NCT00687986) that started in the Netherlands, also in 2008, faced a similar situation as only 22 of the 900 patients planned could be enrolled.

A pooled analysis of the STARS and ROSEL cohorts was published in 2015 [27]. These trials were quite similar in terms of inclusion criteria and interventions, although central tumours were eligible in the STARS trial only (two were included). For the 58 patients enrolled, 31 were treated with SBRT (20 in STARS, 11 in ROSEL) and 27 with surgery. All surgical patients had hilar lymph node dissection and either dissection or sampling of several mediastinal nodal levels. Radiotherapy treatments for peripheral lesions were 54 Gy in three 18 Gy fractions in both trials but could also have been 60 Gy in five fractions in ROSEL trial (which happened

for 5 patients), based on the practice of treating centres. It should be noted that, as often the case in RT, the prescription corresponded to technically slightly different treatments between the two trials.

Although based on few patients, the Chang analysis showed a statistically significant difference in OS with estimated survival rates at 1 and 3 years of 100% (95% CI 100–100) and 95% (85–100) in the SBRT arm for 88% (95% CI 77–100) and 79% (95% CI 64–97) in the surgical group (log rank p = 0.037, HR 0.34, 95% CI 0.017–1.19). Only seven deaths were reported: one patient in the SBRT group who died of cancer progression and six patients in the surgery group (three from lung cancer including a second primary, two from comorbidities and one from attributed to the surgical treatment). Both the STARS and ROSEL trials surgical groups included patient treated with the older thoracotomy technique and not the more actual and less morbid Video-Assisted Thoracoscopy (VATS).

To put things into perspective, a meta-analysis based on 40 SBRT studies (10 prospective, 30 retrospective) and 23 surgery studies (all retrospective), for respectively 4850 and 7071 patients, reported unadjusted 3-year OS for SBRT, lobectomy and sublobar resections of 56.6%, 80.7%, and 77.8%, respectively [28]. After adjustment for suitability for surgery (which integrates comorbidities and age), the estimated survival rates were higher for SBRT patients, although not statistically different, with 89% (95% CI 76–95) vs. 81% (95% CI 76–85) for lobectomy and 80% (95% CI 76–86) for limited lung resection. Currently, the Veteran administration is running a large phase III trial comparing surgery to SBRT (VALOUR trial) [29]. Interesting, the trial includes operable patients with tissue confirmation of NSCLC, staging with FDG-PET/CT, and biopsies of all hilar and/or mediastinal lymph nodes >10 mm that have a SUV >2.5. SBRT doses depend on the tumour location: peripheral tumours will receive either 18 Gy x 3,14 Gy x 4, or 11.5 Gy x 5 fractions, while central tumours will be treated with 10 Gy x 5. The surgery will be either a lobectomy or anatomic pulmonary resection (a segmentectomy) and mediastinal lymph node sampling.

If indeed new decisions regarding patients' management cannot be made based on a post-hoc analysis of two very small sample trials and observational data, the superiority of the surgical approach might not be certain anymore and randomising large numbers of patients is still necessary to provide level-I evidence to answer the question.

The major accrual problem in these trials was attributed to the lack of equipoise in the physicians' minds, or maybe to financial considerations. The two treatment modalities are very different, which can have strong impact on both patients and physicians limiting the acceptability of leaving the treatment choice to chance. Surgery is performed on in-patient basis. As the tumour is removed, it is easier to identify local recurrences. Mediastinal nodal dissection or sampling also allows to identify false negative of PET/CT staging and to guide the decision for an adjuvant treatment. In many SBRT series, the mediastinal evaluation is often limited to the CT or the PET-CT with fewer patients having a mediastinal sampling with Endobronchial Ultrasonography – Transbronchial Needle Aspiration (EBUS–TBNA). Even though an operable patient could be safely operated for salvage in the rare cases of regional relapse, it is probably better to provide the most exhaustive staging possible before choosing the treatment modality.

Another issue is the extra-thoracic failure suggesting to add a systemic treatment. The patients treated currently with a SBRT have often many co-morbidities and are not the good candidate for adjuvant chemotherapy due to the acute toxicity. An answer may be immunotherapy following the impressive positive results for more advanced stages: pembroluzimab, durvalumab and atezolumab are tested in different trials (KEYNOTE-867, PACIFIC-4, SWOG S1914) as an adjuvant

treatment or concurrently with SBRT. An important issue will be the tolerance and the toxicity in this elderly population.

In conclusion, SBRT is an effective treatment modality and a very acceptable alternative to surgery for patients at high surgical risk. For fit patients, a large scale randomised trial is still considered necessary to answer the question: can SBRT replace safely surgery?

3. Stage III non-small cell lung cancer

To-day, most fit patients with a stage III NSCLC are treated with a program of chemoradiotherapy favouring a concurrent approach (CRT) [30]. The results remain far from satisfactory in term of overall survival. This is due to distant metastases and loco-regional failure. Using all our technological developments (IMRT, image guided radiotherapy, PET-CT based planning), local failure is still a major challenge even after doses in excess of 60 Gy. In the recent trial conducted by the RTOG comparing 60 to 74 Gy, the 5 year local failure rates are 49.7% after 60 Gy and 55.4% after 74 Gy [31]. Adding a third modality, surgery, is an appealing approach already proposed many years ago by Strauss and Sugerbacker in their literature review [32]. From a theoretical point of view, there is a clear synergism between radiotherapy and surgery: failure after radiotherapy is often observed in the bulk of the tumour, an area of hypoxia less sensitive to radiation while for surgery, local relapses occur at the margins of resection. Another approach is to improve the systemic treatment by adding immunotherapy.

There are several ways of combining the three modalities: induction chemoradiotherapy (concurrent or sequential) followed by surgery or a sequential approach with an induction chemotherapy followed by surgery and postoperative radiotherapy (PORT). The latter has the advantage to have less toxicity, the ability to evaluate the response to the chemotherapy especially the possible downstaging of mediastinal nodes allowing selecting the best candidate for surgery, the use of full dose of chemotherapy, to treat the possible micro metastatic spread and to have a full pathological evaluation. The drawback is that PORT will be less efficient due to the poor vascularization and the loss of lung volume especially in case of a pneumonectomy. The former allows taking advantage of the radiosensitizing properties of many drugs to obtain a higher rate of tumour response including pathologic complete response but at the price off more surgical complications and more toxicity. The ultimate goal of a three-modality approach is to improve survival while local control and progression free survival (PFS) are only surrogate endpoints.

3.1 Induction chemoradiotherapy before surgery

Many phase II trials reported a higher response rate, more downstaging and pathologic complete response but also more postoperative complications with CRT compared to chemotherapy alone. Using the National Cancer database including more than 11,000 patients with stage III NSCLC, the trimodality approach let to a better outcome with a 5-year survival around 32% [33]. In another analysis from the same database, 1936 patients with a T1, T2 N2 disease were treated with preoperative CRT or induction chemotherapy [34]. The pathologic complete response was higher after CRT (14.2% vs. 4%) but with an increased perioperative mortality and no improvement in OS. One problem with databases even a large one is certainly all the possible biases of patient selections but also the difference in local medical facilities. Indeed, academic facilities were more likely to treat patient with the trimodality than in a community hospital [35]. This is well illustrated by a recent

paper including more than 83,000 patients presenting a stage III NSCLC treated in 1319 facilities. Those treated in a high volume centre (more than 15 patients) were more likely to have surgery or a trimodality and had significantly a lower risk of death [36]. This is one reason to look more to randomised trials to answer the question.

The role of surgery after a concurrent CRT compared to an exclusive CRT approach was tested by two trials conducted in Germany and in the US [37, 38]. Both trials did not observe any difference in OS but only a better local control after a surgical resection or a better PFS. Do we need to include radiotherapy in an induction program? The main advantage of avoiding RT is to reduce the acute toxicity and the surgical complications. Three randomised trials compared induction chemotherapy to a CRT approach for patients presenting with N2 disease initially considered resectable. The Swiss trial is the largest one and the most recent [39]. 232 patients were randomised between induction chemotherapy followed 4 weeks later by surgery and induction chemotherapy followed by RT (44 Gy in 22 fractions and 3 weeks) without any chemotherapy and surgery 3 to 4 weeks later. PFS and OS were not found different between the two arms. A R0 resection was observed in 91% and 81% in the arm with or without RT respectively. The pathologic complete responses were very similar with respectively 16 and 12%. Interestingly, no operative mortality was reported after RT. The main criticism is the use of a sequential approach perhaps explaining the low rate of pathological complete response. Recently, our Spanish colleague reported 99 patients treated with either preoperative CRT or induction chemotherapy. CRT significantly increased the pathologic complete response rate and nodal down staging and reduced the loco-regional recurrence; unfortunately, this did not translate in any survival benefit [40].

PreCRT is a commonly used strategy in patients with superior sulcus tumours. In two phase II trials including 110 and 76 patients, a CRT delivered 45 Gy combined with cisplatin, etoposide or cisplatin, vindesine, mitomycin chemotherapy. A N2 disease was an exclusion criterion. The 5-year survival rates were 44% and 56%, respectively [41, 42]. Important prognostic factors were R0 resection and pathologic complete response. One drawback is the relatively low RT dose in case of no surgery or incomplete resection. Another approach is to deliver a full RT dose. In a Dutch series, 49 patients treated with CRT before surgery (19 patients) or as a definitive treatment (30 patients) [43]. 5-year survival was 33% for the three modalities and 18% for the definitive RT. Clearly, patients selected for the trimodality were highly selected.

3.2 Induction chemotherapy followed by surgery and postoperative radiotherapy

Most trials evaluating PORT were carried out in an era of old radiation technique and not after induction chemotherapy. The meta-analysis showed a detrimental effect of PORT especially for stage I and II disease [44]. Another meta-analysis stratified the trials according to the use of a cobalt 60 unit or a linear accelerator [45]. PORT carried out with a linear accelerator increased OS and local control for stage III disease. Many retrospective analyses from single centre or from large data base look at the impact of PORT for stage III: if local control was improved, the impact on survival led to conflicting results.

RT technique is a key factor to avoid an excessive toxicity. The radiation plans used in the trials included in the meta-analysis were compared to our current RT techniques [46]. The older technique led to poor target coverage and an excessive toxicity. The target coverage reached only 65% and the heart $V30_{Gy}$and the lung $V20_{Gy}$were higher with the technique used in the randomised trials. A Polish study

evaluated the cardio-respiratory functions in patients who did and did not receive modern PORT technique: they observed no increase in non-cancer radiation-induced mortality or deterioration of lung functions [47].

Currently, another issue is the role of PORT after induction chemotherapy for N2 disease since local relapse is a common feature as observed in several prospective phase II series. The cumulative loco regional recurrence rose even to 60% in the Betticher trial including 75 patients treated with upfront chemotherapy followed by surgery [48]. Persistent N2 disease after ICT is a pejorative factor but several questions on PORT remain: the place of PORT according to the pathologic response ypN0 versus ypN2 and PORT only or with sequential or concurrent chemotherapy. The data were coming from retrospective studies but the results of the LungArt trial were just presented at the ESMO congress: this phase III trial compared mediastinal PORT (54 Gy in 27–30 fractions) to no PORT. Patients included had a complete resection with nodal exploration, proven N2 disease and neo or adjuvant chemotherapy. PORT was associated with a non- statistically significant 15% increase in DFS at 3 years but without an OS benefit [49].

3.3 Discussion

All those trials have a major problem: they were conducted many years ago and are not in agreement with our current practice due to technological developments in diagnostic procedure (MR, PET-CT), in radiotherapy and in surgery and to the new drugs available including target agents and immunotherapy. Clearly, those data do not help us to choose between a trimodality and a concurrent chemoradiotherapy as the results suggest similar outcome in term of survival. Furthermore, stage III is a very heterogeneous group of tumours and the TNM has evolved over the years with different stage grouping both for the T and the N components in the different UICC classifications. Many trials have only included N2 patients or stage IIIA while other also included stage IIIB.

Nevertheless, there are a few lessons we have learned. One concern using induction chemotherapy before a local treatment is the delay between its termination and the start of the local treatment: accelerated repopulation of cancer cells and tumour regrowth can occur [50]. This is even more valid when the decision to do the surgery is taken after the induction treatment to see the possibility of a resection with free margins. In case of no resection or incomplete resection, the patient may have not an optimal curative treatment as the preoperative RT dose is often too low to achieve a good local control. Moreover, the addition of a boost delivered after several weeks of RT interruption is not very effective due to tumour repopulation.

The decision between both approaches should be discuss on individual base after a careful patient evaluation with a full staging including PET-CT and brain MR to avoid a futile treatment and an evaluation of patient fitness to undergo surgery or even radiotherapy. Many patients have a long history of tobacco smoking and are suffering from many co-morbidities increasing the risk of complications or even not allowing a surgical resection. The decision is to be taken during a tumour board involving all specialties: the feasibility of a complete resection with free margins should be evaluated; an incomplete resection is by definition a futile thoracotomy and salvage treatments have limited efficacy. Another issue is the possibility to deliver a full course of radiotherapy with concurrent chemotherapy. This implies to be able to deliver doses in excess of 60 Gy or a biological equivalent dose taken into account the tolerance of the different organs at risk including the normal lung but also the heart. Finally yet importantly, an essential parameters are the local treatment facilities and the local clinical expertise but also the discussion with the patient of the pros and cons.

3.4 Immunotherapy with anti PDL1 drugs

If immunotherapy approach was in the past not very successful especially the vaccination strategies; the current approach is to play on T-cell activation or modulation in the tumour or microenvironment using anti-PD-1/PD-L1 drugs. Those drugs have fully changed the pattern of care for stage IV NSCLC with marked improved survival. It was often consider that RT had an immunosuppressive effect. Nowadays, there is a body of evidence suggesting that RT may increase the immune response both locally and systematically [51]. RT may act through a spectrum of cellular and molecular alterations and through the release of tumour-associated antigen. There are now a lot of observations suggesting a synergistic action of RT with anti-immune-checkpoint blockades with anti-PD-(L)1. Experimental data showed an increase in the expression of PD-L1 at the surface of tumoral cells after RT, improving the survival [52].

An interesting observation was seen in the phase I trial with pembrolizumab in stage IV NSCLC: in the phase I trial Keynote-001, patients treated with radiotherapy prior to pembrolizumab had a better survival regardless of the site irradiated [53]. In case of chest RT, 3 patients out of 24 developed a grade 3 lung toxicity after prior RT compared to one 1 out of 73 for pembroluzimab.

PACIFIC is a large scale phase III trial comparing durvalumab (an anti-PD-L1 antibody) to a placebo as a consolidation treatment after chemoradiotherapy [54]. Patients had to have received two cycles of cisplatin-based chemotherapy and a response or stable disease. The randomisation was performed 1 to 42 days after the end of radiotherapy. Few data are available regarding the initial chemoradiotherapy. Durvalumab was administered every 2 weeks for up to 12 months. The three year OS was 66.3% versus 43.5% for the placebo arm, results highly statistically significant. The PD-L1 status was not known for all patients but a post hoc analysis found similar results regardless of PD-L1 status. The lung toxicity was 13% after durvalumab and 8% in the placebo arm but grade 3 pneumonitis rates were very similar (3.4% vs. 2.6%). It is also not easy to compare the observed survival to others series as randomisation in PACIFIC is done after initial chemoradiotherapy, excluding those patients progressing or not tolerating the initial treatment. Nevertheless, this trial has changed our daily practice by adding durvalumab quickly after the end of chemoradiotherapy in locally advanced NSCLC.

The question of finding the best combination of immunotherapy and radiotherapy remains. Experimental data suggest better results when the drug is given during radiotherapy rather after its end: this was seen in an experimental study conducted on mice with colon carcinoma CT26 tumours [52]. One concern is the risk of increased toxicity especially at the level of lungs and heart: pneumonia is a classical complication of anti-PD-L1 drugs but also after chest radiotherapy. The NICOLAS phase II trial was designed specifically to answer this question [55]. Patients were treated with three cycles of a cisplatin-based chemotherapy and radiotherapy started with the second cycle together with nivolumab given up to 1 year. The endpoint was grade 3 or more pneumonitis observed during 6 months after the end of RT. Amongst the 80 patients included, 8 developed grade 3 pneumonitis after radiotherapy.

Radiation may also release tumoral antigens allowing a better recognition by the immune system but also acting against tumour cells outside the radiation field (the so called “abscopal effect”). In the Pembroluzimab-RT phase II trial, patients with stage IV NSCLC were randomised between pembroluzimab alone and pembroluzimab given after SBRT to a single metastatic site [56]. The goal was to test if SBRT increases the response rate: 17 patients out of 36 presented a response with the combined approach vs. 9 out of 40 patients in the pembroluzimab alone arm. The

disease control rates at 12 weeks were respectively 63% vs. 40%. A retrospective study included 117 patients: 54 received SBRT with concurrent immune checkpoint inhibition and 63 SBRT alone. The risk of grade 3 radiation pneumonitis was higher in the combined approach (10.7% vs. 0%) [57]. In patients with a oligometastatic disease, the addition of a local treatment such as SBRT is a very exciting approach but a close monitoring for pneumonitis should be considered. Several trials are currently on-going.

Ultimately, there are a lot of unresolved questions: what is the optimal dose (low or high as the one used with SBRT), the actual volume to be treated, the timing…? Clearly, it is not easy to use a SBRT approach in stage III NSCLC as it is done for smaller metastatic lesions in stage IV NSCLC; the total volume to irradiate in stage III disease is much larger and could potentially lead to an excessive toxicity. Another issue lies in the volume of circulating immune cells during RT: the current technique to irradiate stage III NSCLC uses IMRT techniques delivering very low doses spread across large normal tissue volumes which may decrease the lymphocytes counts (a very sensitive cell to low RT dose), and subsequently the immune response. A retrospective study has observed a lower survival in case of lower absolute lymphocyte blood count [58]. So, blood-containing organs such as great vessels, heart and bone marrow may become a new organ at risk to spare in the future. Ideally, there is an urgent need to find a biomarker allowing to better select patients candidate for a combined approach in order to avoid futile treatments and also to decrease the expenses of those new treatments.

4. Small cell lung cancer (SCLC)

SCLC accounts for around 15% of all diagnosed lung cancers worldwide [59]. It is a highly aggressive, undifferentiated neoplasia characterised by a high proliferation rate and early metastatic spread. Although SCLC is very responsive to initial chemotherapy and radiotherapy, early recurrences are common and the prognosis of SCLC remains poor with 5-year overall survival rates of under 10% [60].

In the late 60's, SCLC was staged as limited disease to the thorax (LS) or extensive stage (ES) according to the Veterans' Affairs Lung Study Group classification and later modified by the International Association for the Study of Lung (IASLC) [61, 62]. Interestingly, limited disease include tumour confined to the ipsilateral hemithorax and regional lymph nodes in order to be encompassed in a radiation field. More recently, the IASLC recommends to use the revised TNM staging classification for lung cancer (American Joint Committee on Cancer AJCC 7th edition) for clinical decision making and clinical trials instead of the LS- and ES-categories, as it better discriminate the prognostic impact [63, 64].

4.1 Limited stage-small cell lung cancer (LS-SCLC)

CRT is the current standard of care [65]. In the early 90's two meta-analyses have outlined the benefit of adding chest RT to chemotherapy [66, 67]. The Pignon meta-analysis was the most interesting due to the utilisation of the patient individual data from 13 randomised trials: chest RT improved the OS by 5.4% at 3 years but at the price of more esophagitis [67]. The benefit was greater for patients under 55 years (the relative risk of death was 0.72), than for those over 70 years. Two meta-analyses of randomised controlled trials have looked to the timing of chemotherapy and RT: concurrent CRT should start as early as the 1st or 2nd cycle of platinum-based chemotherapy to be more effective in terms of survival, compared to delaying the start of RT to the 3rd cycle or later [68, 69].

Another question was the optimal dose and fractionation. In the Intergroup 0096 trial, 471 patients were randomised between 45 Gy in 30 fractions twice daily (BiD), in a total of 3 weeks and 45 Gy in 25 fractions, once a day in 5 weeks. In both arm, RT started with the first of the 4 cycles of chemotherapy (cisplatin and etoposide) [70]. Overall survival rates at 2 and 5 years were respectively 41 vs. 47%, and 16 vs. 26% ($p = 0.04$) in favour of the BiD treatment. The drawback was more acute toxicity, mainly grade 3–4 esophagitis, from 16–32% with the BiD but without any increase in the risk of grade 3 or higher pneumonitis (6% in both arms). Given the highly proliferative nature of SCLC, a shorter time between RT fractions and a shorter overall treatment time (3 weeks instead of 5) could explain the better results of BiD fractionation against tumour repopulation. However, the major limitation in the design of the Turrisi trial is that the two arms have not the same biologically equivalent dose, a higher dose for the BiD arm. Nevertheless, this pivotal trial confirmed the impact of a better local turning in a benefit of survival and cure. However, many radiation oncology centres did not use the BiD fractionation because of the increased oesophageal toxicity and the inconvenience for the patient linked to have two treatments on the same day with an interval of minimum 6 h between the 2 fractions but also for busy radiation facilities [71].

The Japan Clinical Oncology group JCO 9104 phase III trial compared a concurrent CRT to a sequential CRT and included 231 patients. Chest RT was delivered with the first of the 4 cycles of chemotherapy (cisplatine and etoposide) or one month after the last cycle. The chest RT was a BiD delivering 45 Gy in 30 fractions over 3 weeks [72]. The median OS was significantly better for the concurrent arm compared to the sequential one (27.2 vs. 19.7 months, $p = 0.02$ after adjustment for performance status, age, and stage in a Cox model). The oesophageal toxicity was quite similar between the two arms (4% vs. 9% for sequential vs. concurrent, respectively) but the haematological toxicity was increased with the concurrent treatment (grade 3–4 leukopenia: 88% vs. 54%, $p < 0.001$).

The CONVERT trial designed to answer the question rose by the Turrisi trial and included 547 patients [73]. The trial compared a BiD approach (45 Gy delivered in 30 fractions over 3 weeks) to an escalated daily RT (66 Gy in 33 fractions over 6.5 weeks). The study was designed to show superiority for the once daily experimental arm over the control BiD arm. While there was no difference in toxicity and OS between the two groups, the BiD arm showed a trend toward an improved median OS (30 vs. 25 months, $p = 0.14$), leading to the conclusion that BiD remains the standard of care. Still, a lot of radiotherapy centres prefer to use the more convenient once daily fractionation (at the total dose of 66 Gy) since survival and toxicity were similar in both arms [74]. A recent Scandinavian randomised phase II trial presented at the annual ASCO meeting randomised between high-dose BiD CRT of 60 Gy in 40 fractions (4 weeks) vs. 45 Gy in 30 fractions (3 weeks), both arms with 4 courses of platinum. The survival rate at 2 years were in favour of the 60 Gy arm (73% vs. 46%, $p = 0.001$), and they had a significantly longer median OS (42 months vs. 23 months; HR 0.63, $p = 0.031$) without any significant differences in term of toxicity (esophagitis or grade 3–4 pneumonitis) [75]. Those promising results need a confirmation through a phase III trial including more than the 160 patients. The RTOG is conducting a three arm trial comparing 70 Gy in 7 weeks, 61.2 Gy delivered with one fraction daily of 1.8 Gy for 16 days followed by 1.8 Gy BiD for 9 days to the classical 45 Gy in 3 weeks BiD (RTOG 0538 trial); the second arm was prematurely closed.

Durvalumab has also showed activity for extensive SCLC and is tested as adjuvant treatment for limited disease with or without tremalimumab (The

Adriatic trial). In a phase III trial, Atezolumab is delivered concurrently with chest RT and cisplatine-etoposide(NRG-LU005). The results of the Stimuli trial were presented at the last ESMO congress. After the end of chemoradiotherapy including also PCI, patients were randomised to receive ipilinumab and nivolumab for 12 months. No difference was observed in PFS neither in OS but increase the toxicity [76].

There is also the question of the target volume for radiotherapy: an elective nodal irradiation including the full mediastinum to treat the possible microscopic nodal sites was typically used in the past but at the cost of increased toxicity, an era of no PET-CT. In several prospective studies, the RT volume was limited to the known macroscopic disease as seen on a PET-CT and failures outside were a rare event: 3% and 2% in two different series of 60 patients from the Netherlands and the USA [77, 78].

Currently, the indications for surgery are limited to the very limited disease mainly stage I and II disease for fit patients and adjuvant chemotherapy is then necessary.

4.2 Extensive stage-small cell lung cancer (ES-SCLC)

The treatment cornerstone is a platinum-based chemotherapy regimens including cisplatin or carboplatin and etoposide combined with immunotherapy. This first line treatment yields often excellent initial responses and improved survival. However, recurrent or persistent intrathoracic disease is observed in more than 75% patients and local control remains a major problem during the first year of follow-up. A phase III study compared chest radiotherapy (54 Gy in 38 fractions over 18 days with concurrent cisplatin/etoposide) to only additional cycles of chemotherapy [79]. Patients had to have obtained a complete response at the metastatic sites and a complete or partial response in the thorax. The combined approach led to a better survival: median survival time of 17 months vs. 11 months and a 5-year survival rate of 9.1% vs. 3.7%.

The CREST trial randomised 498 patients to evaluate the benefit in term of OS by adding chest RT (30 Gy in 10 fractions over 2 weeks) as a local consolidation after first line cisplatin-based chemotherapy [80]. Although the study failed to achieve its initial endpoint of survival at 1-year, an interesting observation is certainly the slight survival improvement seen at 2 years: 13% vs. 3%, ($p = 0.004$). Importantly, RT allowed a marked 50% reduction in loco-regional recurrences. The radiation target volumes included the post-chemotherapy tumour and the nodal stations initially involved before the start of first line chemotherapy. These results lead to consider consolidative chest RT as a standard treatment after a response to chemotherapy, in addition to prophylactic cranial radiotherapy. Nevertheless, this is now questionable: two trials have showed a survival improvement by adding atezolumab to a platinum doublet [81, 82]. A trial is now on-going to evaluate the role of consolidative radiotherapy to up to 5 sites after a partial response or stable disease after a doublet of cisplatinum with atezolumab (Raptor trial).

4.3 Prophylactic cranial irradiation (PCI)

Brain metastases (BM) represent a major challenge in the management of SCLC, with an incidence as high as 50% at 2 years. The brain is considered a sanctuary site due to the blood brain barrier and the limited access for most available drugs. Based on prior experiences in leukaemia, Heine Hansen introduced in 1973 the concept of PCI for SCLC [83]. The aim of PCI is to prevent BM, avoiding the potential neurological complications, and ultimately to improve survival.

Several randomised trials demonstrated that PCI decreased the incidence of BM and Auperin's meta-analysis using the individual data of 987 SCLC patients from 7 randomised trials confirmed clearly the survival benefits (both OS survival and PFS): PCI reduced by 25% the incidence of BM and increased the survival by 5,4% at 3 years (20,7% vs. 15,3%) [84–86]. Most patients had a limited-stage disease (85%) considered in complete response to the initial chemotherapy. A more recent meta-analysis including 1983 patients from 16 randomised trials showed a similar survival benefit without any impact of disease extent [87]. One problem with many trials is the lack of brain imaging in the initial staging and the CR evaluation: BM incidence is reduced by PCI from 53–40% in the absence of brain imaging while it reduces BM from 33 to 10% in case of brain CT-scan [88]. Today, MRI has increased the detection rate of BM from 10 to 24%. Importantly, the patients detected with BM by CT scan were often symptomatic while they had no symptoms in case of brain MRI.

The optimal radiation dose for PCI was tested by the large Intergroup PCI99–01 trial: 720 patients were randomised between 25 Gy in 10 fractions in 2 weeks vs. 36 Gy in 18 daily fractions or 24 BiD fractions [89]. This study failed to show any benefit with a higher radiation dose, neither on the incidence of BM or in survival; furthermore, the incidence of brain metastases remained high (35% at 3 years). Therefore, the recommended radiation schedule for PCI remains 25 Gy in 10 fractions delivered in 2 weeks.

Toxicity remains a major concern: acute (hair loss, fatigue,..) or late (hearing and cognitive impairment, dementia, leukoencephalopathy,...). The cognitive functions were evaluated before, at 6 and 12 months after PCI with the self-reported cognitive functions tests of EORTC: a threefold cognitive decline was observed at 6 months as well as at 12 months after PCI [90]. Those neurocognitive functions are highly depending on the hippocampus area. Currently trials are on-going to evaluate the efficacy and safety of a PCI using a hippocampus avoidance technique. Most guidelines recommend PCI for patients in complete response but it is also challenge by a close brain MRI follow-up [91, 92].

For patients presenting an extensive disease, PCI is also proposed after a response to platinum-based chemotherapy. This is based on the results of the EORTC phase III trial: patients with any response to chemotherapy were randomised between PCI and no PCI. PCI reduced the incidence of BM from 40–16% at one year, leading to a significant survival increase (13–27%) [93]. A pooled analysis of the North Central Cancer Treatment Group (NCCTG) trials including 421 patients observed similar results [94].

In contrast, a recent Japanese phase III trial randomised patients between PCI (25 Gy in 10 fractions) or no PCI after any response to initial chemotherapy and a recent MRI showing no BM [95]. The observation arm required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment. PCI reduced the incidence of BM but without any overall survival benefit: median survival was 11.6 months in the PCI group and 13.7 months in the observation group (HR = 1.27, 95% CI = 0.96–1.68; p = 0.094). Consequently, the Japan Lung Cancer Society removed PCI from their treatment guidelines in ES-SCLC. In those two trials, the patient population is quite different just by looking to the difference in survival. This trial and the concerns on PCI toxicity have led the SWOG to launch a trial comparing PCI to a MRI surveillance for extensive but also limited small cell lung cancer.

5. Conclusion

Over the past few years, major improvements have been made in the management of lung cancer due to the introduction of SBRT and immunotherapy. Both

have changed the daily practice not only of early stage lung cancer but also for stage IV diseases. A major development in the future will be to include (SB) RT in the management of metastatic lung cancer to promote the immune system but also to treat local lung tumours. So, there is still a long way to understand how to optimise those modalities for each individual patient but also to understand the disease.

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