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The Role of Radiotherapy in the Management of Non Small Cell Lung Cancers

Fatma Elloumi[1], Lilia Ghorbal[1*], Mayada Bourmeche[1], Ahmed Bebou[1], Hanene Ben Salah[1] and Jamel Daoud[1]

[1]Radiation Oncology Department, Habib Bourguiba University Hospital, Sfax, Tunisia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Non small cells carcinoma represents the most frequent histological subtype in lung cancers.
We report, through a review of literature, the indications of radiotherapy in patients presenting with non metastatic lung non small cell carcinoma.
Postoperative radiotherapy seemed to improve local control, without any benefit on overall survival. Therapeutic indications for N2 stage are still controversial. Concomitant radiotherapy and chemotherapy is the standard of care in non operable non small cell lung cancer. Chemotherapy protocols should include platinium. Stereotaxic radiotherapy is indicated for patients with non operable small tumors.
Improvement in delivering systems in radiotherapy improves the treatment results in non small cell lung cancers.
Radiotherapy has an important role in the treatment of this entity. Conformal radiotherapy tested dose escalation with improvement in local control and preserved organs at risk.

Keywords: Non small cell; lung; cancer; external radiotherapy.

**Corresponding author: E-mail: lilia.ghorbal@yahoo.fr;*

1. INTRODUCTION

The non small cells lung carcinoma (NSCLC) will remain the first malignant tumor in humans in the world and especially in emerging countries, including Tunisia, due to an anti-smoking policy, often proposed, but not implemented. Most of the 2000 annual cases identified in Tunisia are locally advanced (stages III) or metastatic (stages IV) [1,2]. Radiotherapy (RT) therefore remains one of the major therapeutic weapons in thoracic oncology in the management of NSCLC [3]. It is often associated concomitantly with chemotherapy (CT), especially in cases of locally advanced inoperable forms. Postoperative adjuvant RT remains a subject of controversy. Progress has been made in terms of imaging coupled with treatment machines, in particular scanners and PET scans (Positron Emission Tomography) but also in conformational radiotherapy techniques to ensure better local control while avoiding as much as possible irradiation of healthy tissue. Our goal is to review the indications for radiotherapy for patients with NSCLC that is non-metastatic, whether operable or inoperable.

2. GENERAL PRINCIPLES OF THORACIC RADIOTHERAPY

The progress made in radiotherapy is mainly due to advances in imaging techniques, especially the scanner and PET-scan allowing better definition and evaluation of the volumes to be treated, but also to innovations in irradiation techniques, especially conformational radiotherapy and respiratory control [3].

The definition of the target volume has been the subject of much controversy regarding the response to chemotherapy and prophylactic irradiation of lymph node areas.

The dose to be delivered depends on the histological type and the therapeutic indication depending on whether it is an adjuvant treatment or not. However, the proximity of many critical organs can lead to modulating the prescribed dose.

The recommended dose for conformational radiotherapy is greater than 66 Gy. Fractionation is often classic with 5 daily sessions of 1.8 to 2 Gy per week [3].

Combination with chemotherapy, especially concomitant combinations, may increase toxicity. Therefore, it is necessary to take into account the type of drugs used, the doses administered and the volumes to be irradiated while respecting the chronology of the combination.

3. MEDIASTINAL POSTOPERATIVE RADIOTHERAPY

Evaluated by multiple randomized trials, postoperative irradiation seemed to improve local control without benefiting overall survival [4]. The rationale for this irradiation was a high relapse rate after surgery alone.

The PORT meta-analysis made it possible to bring together the data from 9 randomized trials, several of which are very old [5] with a number of 2128 patients collected between 1966 and 1995, of which 808 patients had stage III, irradiated using a conventional technique, with large target volumes. The inclusion criteria included complete resection and correct randomization. Overall survival at 2 years was 48% in the postoperative radiotherapy arm and 55% in the surgery alone arm. There was no gain in terms of locoregional control. The subgroup study showed a deleterious effect of postoperative radiotherapy for stages I and II in case of complete excision. The update of this meta-analysis, published in 2005 after the inclusion of a 10th study, showed the same results [6].

The question for stages III remained open. The effect of radiotherapy for tumors with N2 lymph node involvement was neither deleterious nor clearly beneficial [5]. Likewise, the study of the subgroups of the ANITA trial [7] showed a positive effect on the 5-year survival of postoperative radiotherapy combined with chemotherapy for the N2 groups.

The analysis of these results was subject to several criticisms regarding the patient selection criteria which varied from one study to another, the definition of complete excision, the surgical techniques and the modalities of irradiation.

Locoregional relapses in stages T1 / T2 N0 are in the order of 5 to 10% while those in stages III are much more frequent (> 30%). New randomized trials with new irradiation techniques are needed. The role of postoperative radiotherapy will be better defined after the results of the LUNGART trial currently underway, randomizing patients with complete resection and with N2 mediastinal invasion between conformational postoperative irradiation limited to the mediastinum at a dose of 54 Gy and monitoring.

4. PLACE OF RADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED NON- RESECABLE FORMS

Until the 1980s, the standard treatment for locally advanced lung cancer was chest radiotherapy alone. Its superiority over palliative care was demonstrated in the 1968 VETERANS Affairs group trial [8]. The results of radiotherapy alone were disappointing with survival not exceeding 20% at 2 years and 5% at 5 years.

Deaths are linked to lack of local control and / or metastases. Therefore, the combinations of chemotherapy and radiotherapy were tested in the mid-1980s. The superiority of the combination of radiotherapy and chemotherapy has been demonstrated compared to treatment by radiotherapy or chemotherapy alone: the combination of chemotherapy radiotherapy has improved local and remote tumor control with a survival rate of 20% and 40% at five years [9-12].

The sequential and concomitant associations were compared with radiotherapy alone in several trials [9-12]. The benefit of sequential chemotherapy was confirmed as early as 1995 by a meta-analysis [13]. An increase in the overall survival rate of 2% at 5 years was found with the 2 types of combination.

Better local control was reported with the concomitant regimen, the theoretical advantages of which were better temporal and spatial cooperation allowing a reduction in the emergence of resistant clones [14].

Therefore, six randomized trials were interested in comparing the two types of association. Only four trials showed the superiority of the concomitant arm over the sequential arm [15-19].

These results were confirmed by the Aupérine meta-analysis. The update published in 2010 found a benefit of 4.5% in terms of overall 5-year survival from the concomitant combination [20]. The toxicity was increased with the concomitant combination. Acute neutropenia and esophagitis have been reported in more than 50% and 20% of patients, respectively. These data were supported by another meta-analysis [21].

The combination of radiotherapy and concomitant chemotherapy has since become the gold standard treatment for patients with locally advanced NSCLC in general condition.

The choice of molecules tested concomitantly with radiotherapy was based on the results of tests in the metastatic phase. The protocols used have associated a platinum salt with one or even two molecules. Gemcitabine, paclitaxel and navelbine had the same efficacy in combination with radiotherapy according to the study by Vokes et al [22].

Gemcitabine, classically contraindicated concomitantly with radiotherapy, is a powerful radio sensitizer which can be used with respect to maximum doses and the total dose of radiotherapy [23].
Consolidation chemotherapy after concomitant chemoradiotherapy was the best therapeutic sequence compared to the sequential combination and the concomitant protocol preceded by induction chemotherapy. Its superiority has been demonstrated in terms of local and remote control and survival, but at the cost of increased toxicity [24].

The benefit of induction chemotherapy before chemotherapy and concomitant radiotherapy has not been demonstrated in 2 phase III trials [11, 24].

5. PLACE OF RADIOTHERAPY IN THE TREATMENT OF SMALL TUMORS IN INOPERABLE PATIENTS

Radiotherapy is an alternative to surgical treatment in patients with small resectable lesions but having a contraindication to surgery. Qiao et al in 2003 showed that irradiation carried out with good ballistics and at biologically high doses greatly good local control to be obtained, especially using the technique of stereotaxic radiotherapy [25-26].

Onishi et al, reported a correlation between the dose delivered by stereotaxic radiotherapy and local control as well as 5-year survival [27]. He studied data from 257 stage I patients after a median follow-up of 38 months. The local relapse rate was 8.4% for a dose equivalent greater than 100 Gy and 42.9% for a dose equivalent less than 100 Gy. Likewise, 5-year survival increases from 70 to 30%. if the dose is less than 100 Gy.

6. OPTIMIZATION OF RADIOTHERAPY MODALITIES

The technical modalities of conformational radiotherapy have undergone changes over the years, ranging from the acquisition of anatomical

data to field ballistics, including the definition of the volumes to be irradiated and the prescribed doses.

6.1 Acquisition of Anatomical Data

Carrying out radiotherapy for lung tumors is a real challenge by trying to respect the doses of tolerance to healthy organs and to take into account the movements of the tumor and the organs during the respiratory cycle while ensuring optimal coverage of the target volumes.

Anatomical data is acquired using a scanner in the treatment position with an injection of a contrast product if there is no contraindication. A respiratory servo system is recommended for tumors of the middle or lower chest [28]. In the planning scanner, MRI for tumors of the apex and PET can be merged. Technological advances, in particular PET, imaging by intensity modulation (IMRT) and IGRT [28-29] make it possible to precisely define the margins in relation to tumors, to reduce the rate of late effects linked to the tumor irradiation.

FDG PET is a great help in defining tumor volume, particularly lymph node [30-32]. It also makes it possible to distinguish between a tumor and a non-tumor tissue, to carry out selective irradiation of pathological mediastinal lymph nodes and to detect extra-thoracic metastases.

6.2 Definition of Target Volumes

The macroscopic tumor volume or GTV (Gross Tumor Volume): includes the pulmonary and lymph node tumor volumes visible on the scanner. Prophylactic supraclavicular irradiation is only indicated for apical tumors or in cases of upper mediastinal invasion [33-34].

In the absence of trials looking at the volumes to be treated after chemotherapy, it is recommended to take the volume before chemotherapy [34]. It is recommended to consider as tumoral the nodes whose small axis is greater than one centimeter or fixed on the PET [32].

6.3 The Anatomo-Clinical Target Volume or CTV (Clinical Target Volume)

It takes into account infra-radiological extensions. A margin between 5 and 8 mm is defined around the GTV. This margin is variable according to the histological type [35-37].

Likewise for lymph nodes, a margin of 3 mm is recommended for nodes less than 2 cm in diameter and 8 mm for nodes with a short axis of more than 2 cm [36].

The predicted target volume or PTV: takes into account the movements of the organs and the patient and also the positioning uncertainties which varies between 5 and 10 mm depending on the teams and the techniques used [33]. The ICRU (International Commission on Radiation Units) has divided this margin into two parts. A first margin around the CTV takes into account lung movements and defines the ITV (Internal Target Volume). The irradiation technique with respiratory control reduces the uncertainties associated with respiration for basal and mid-lobe tumors [29,30]. The second margin is linked to positioning uncertainties and depends on the means of restraint and the technique adopted.

6.4 Prescription of the Dose

The dose depends on the therapeutic sequence. A dose of 66 to 70 Gy is recommended in the event of exclusive radiotherapy but the local recurrence rates remain high, around 80% [14]. Thanks to the development of conformational radiotherapy techniques, several trials evaluating dose escalation have been initiated. A correlation between the increase in the dose and the rate of local control was found with even a gain in survival in some trials [5,38-39].

The modification of fractionation has been tested in randomized studies. A meta-analysis reported an absolute gain of 2.5% in overall 5-year survival using hyperfractionation compared to conventional fractionation; however, acute esophageal toxicity is increased [40].

In the event of postoperative radiotherapy, a dose of 46 to 56 Gy is recommended on the R1 resection areas or on the mediastinum for pN2 [5,41-42].

6.5 Dose Constraints

They represent doses that should not be exceeded and which may cause toxicities.

- The healthy lung: conventionally, the parenchyma of both lungs is taken into consideration, from which the estimated target volume is subtracted. The percentage of this volume receiving a dose of 20 Gy should be less than 30% [41]. After

pneumonectomy, the remaining lung V20 should be less than 20. The average dose should not exceed 15 to 20 Gy.

- The heart: the cardiac volume receiving 40 Gy must not exceed 30% with particular attention to subjects at cardiac risk [42].
- The marrow: it is recommended not to exceed the dose of 45 Gy.
- The brachial plexus: the problem often arises with tumors of the apex, however a maximum dose of 55 Gy must be observed.
- The esophagus: the volume receiving 50 Gy must be less than 35%. These values must be reconsidered in the event of concomitant chemotherapy and radiotherapy [43- 45].

7. CONCLUSION

Radiation therapy is one of the effective therapies in thoracic oncology. The advent of conformation techniques has made it possible to test the dose escalation route ensuring better local control while respecting the organs at risk and therefore an acceptable tolerance. The combination of chemotherapy and radiotherapy is also a breakthrough in terms of local and remote control. These results call for more trials to better support the indications for radiotherapy, especially postoperatively.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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