ADJUVANT TREATMENTS FOR NON-SMALL CELL LUNG CANCER

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Surgery remains the cornerstone for the curative treatment of non-small cell lung cancer (NSCLC). Long-term survival depends on different prognostic factors including the tumour extent (the T and N stage) and the quality of the surgical resection (complete vs. incomplete resection, the type of mediastinal exploration). Nevertheless, only one-third of all operated patients will be metastases alive 5 years after the surgical resection. Failures are due to a loco-regional relapse, distant metastases or a second primary cancer related to the long story of tobacco abuse. The pattern of failure analysis should decide on the type of adjuvant treatment: a loco regional modality or a form of systemic treatment such as chemotherapy or immunotherapy.

Adjuvant Chemotherapy

For more than four decades in many trials the value of adjuvant chemotherapy after surgery without helping to clearly clarify the issue has been tested. Most trials did not show any benefit or even had a negative impact; some small trials claimed survival benefits. The meta-analysis conducted in the mid nineties by the Cambridge group included 14 trials comparing surgery vs. surgery plus chemotherapy for a total of 4357 patients and 7 trials evaluating the role of chemo-therapy after surgery and postoperative radiotherapy for a total of 807 patients [1]. This metaanalysis was based on a review of updated data of individual patients. For the first group of trials without postoperative radiotherapy, the use of a long term alkylating agent (cytoxan, nitro-sourea…) led to a 15% increase in the risk of death; this was reflected in an absolute detriment due to the chemotherapy of 4% at 2 years and 5% at 5 years. For eight more recent trials using a cisplatine-based chemotherapy, there was a trend in favor of chemotherapy with an absolute benefit at 2 and 5 years of 3 and 5% respectively. Those differences did not show a statis-tically significant difference. The same figures were observed for the trials where chemotherapy was applied after surgery and postoperative radiotherapy: the sur-vival benefit was in the range of 2% at five years.

The Cambridge metaanalysis was the starting point for several randomized trials worldwide such as ANITA in France, ALPI in Italy and IALT worldwide. The main feature of those trials is that they use a cisplatine based chemotherapy and recruit thousands of patients so as to show a small but very important benefit due to the high number of patients at risk.

The recent American trial of Keller et al. compared postoperative radiotherapy alone with a combined chemo-radio-therapy approach for completely resected stage II or IIIa disease [2,3]. The trial includes 488 patients. The chemotherapy consisted of cisplatin and etoposide administered for 4 cycles with the first two cycles given concurrently with radio-therapy and the chest radiotherapy delivered 50.4 Gy in 28 daily fractions. No difference was observed between two arms. The only important prognostic factor was the type of mediastinal exploration: sampling vs. radical dissection [3]. Sampling dissection included a removal of at least one lymph node at levels 4,7 and 10 during the right thoracotomy, and at levels 5 and/ or 6 and 7 during the left thoracotomy, whereas radical resection required a complete removal of all lymph nodes at those levels. Among 222 patients with N2 disease, multiple

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levels of N2 were documented in 30% of patients with complete mediastinal dissection, and in 12% of patients with systematic sampling. In this nonrandommized comparison, the mediastinal complete dissection led to a survival benefit for patients with right side lung tumours. The problem of sampling vs. radical dissection was the subject of only one trial: 169 patients were randomized between a lymph node sampling and a systematic mediastinal dissection [4]. There was no difference in the overall survival rate although the number of local recurrences was reduced after mediastinal dissection. Nevertheless, mediastinal dissection yields a better local control and survival for patients with pathological N1 or limited N2 disease: local recurrence dropped from 44.8% after sampling to 29% after radical dissection [4].

Another problem involved in adjuvant chemotherapy after surgery is the patient's compliance: in the Keller trial, 69% of 232 patients studied received all four cycles of chemotherapy. Toxicity and patient's refusal were the common causes for the failure in completing the programme. The general trend favours a neoadjuvant approach even for stage I disease, but additional clinical studies are needed to confirm the results of the French trial [5].

Adjuvant postoperative radiotherapy

For the last four decades, postoperative radiotherapy has been evaluated in many randomized trials without a clear result as to its efficacy. Does the recently published metaanalysis definitively answer the question of efficacy? A simplified view of each individual trial and the meta-analysis will lead to the following conclusion: postoperative radiotherapy is harmful and ineffective for a completely resected lung cancer. Indeed, the adverse impact of postoperative irradiation has resulted in an absolute detriment of 7% at 2 years and 5 years. The metaanalysis included individual data on 2128 patients in nine randomized trials; of which one has never been published, or presented as an abstract (the trial conducted by the European Organization for Research and Treatment of Cancer) [6].

Is there any place nowadays for postoperative irradiation after complete resection of a non-small cell lung cancer ? The above metaanalysis and the review of all the randomized trials, including those which are not embraced by the meta-analysis require a more critical analysis (*Table 1*) [6-17]. The randomized trials were conducted over a period of three decades. The criteria for patient selection varied from one trial to another: from stage I to stage III, from squamous cell to all histology. The definition of complete resection was not the same in all trials: in the Lung Cancer Study Group trial, complete resection implied that the last nodal station removed in the cephalic direction was free of tumour [13]. Furthermore, the quality of the surgical resection was not certainly the same in all trials, especiallly regarding the mediastinal exploration.

Table 1. Trials of postoperative thoracic radiotherapy.

Authors	Dose Pts	Radiation N°	Pathology Selection	Surgery	Patient	Survival
Paterson	45Gy/4w	202	All	Pneum.	NO N+	No Diff.
Bangma	45Gy/5w	73	All	All	NO N+	No Diff.
Van Houtte	60Gy/6w	224	All	All	NO	No Diff.
Israel	45Gy/4.5w	392	Sq.c.	All	N0 N+	No Diff.*
Debevec	30Gy/2w	74	NSC	All	N+	No Diff.*
Feng	60Gy/6w	366	NSC	All	N+	No Diff.*
LCSG	50Gy/5w	230	Sq.c.	All	N+	No Diff.*
MRC$	40Gy/3w	308	NSC	All	StageII,III	No Diff.*
Laffite	45-60Gy/4-6w	163	NSC	All	T2N0	No Diff.
Dautzenberg	60Gy/6w	728	NSC	All	Stage I-III	No Diff.
Granone	50Gy/5w	104	NSC	All	Stage I	No Diff.

° Lung Cancer Study Group $ Medical Research Council

* Those studies show a better local control in case of positive mediastinal lymph nodes

The technique of postoperative radiation is another important issue: in the Brussels study, patients were treated with a Co 60 source delivering a dose of 60 Gy [9]. This was at a time when dose calculation was not performed using a modern treatment-planning unit, and no CT was available. The Medical Research Council trial delivered a dose of 40 Gy in 3 weeks, with a posterior spinal block [14]. In the Dautzenberg trial, a dose of 60 Gy was delivered with a linear accelerator, or even a cobalt unit using a 4 fields technique, 4 or 5 times per week was employed [16].

Last but not least, some interesting observations were reported from this metaanalysis and the Dautzenberg trial [6,16]. In the analysis by stage or by nodal status, the adverse impact of postoperative irradiation was mainly seen for stage I disease, and it completely disappeared for stage III [6]. Two explanations are possible: the short life expectancy of patients with stage III disease did not make it possible to see the detrimental effect of radiation or the therapeutic effect of radiation that would compensate for it's the negative impact. The former can easily be refuted: one of the main causes of late toxicity induced by postoperative irradiation is related to lung damage; since pneumonia and lung fibrosis occur within the first year of observation. Dautzenberg et al. reported non-cancer related deaths corresponding to the daily radiation dose: 7% for the control group, 16% for less than 2 Gy, 18% for 2 Gy and 26% for more than 2 Gy. [16]. In that trial, a dose of 60 Gy was delivered over six weeks from a linear accelerator or a cobalt 60 unit without lung factor correction. The initial part delivered a dose of 40 Gy to a large volume including the supraclavicular areas with anterior and posterior fields, while the remaining 20 Gy were given using oblique or lateral fields limited to the bronchial stump, hilum and mediastinum. The treatment required 4 or 5 sessions per week. The technique used (lateral fields, a large volume, a higher daily dose, a cobalt unit, absence of lung factor correction etc.) may easily explain the negative impact of irradiation and the higher non-cancer related death rate for daily doses above 2 Gy.

Postoperative irradiation for lung cancer represents a form of challenge for a radiation oncologist: our aim is to prevent a locoregional relapse and to avoid inducing life threatening complications to different vital organs such as: the lung, the spinal cord and the heart. Furthermore, patients have already weakened their lung functions due to surgery and a long history of tobacco abuse. Large daily fractions and volumes, a high total dose and a poor radiation technique may account for the negative results observed in the metaanalysis. Any extension of margins or volumes of elective nodal irradiation will increase the amount of the normal tissue irradiated, especially the esophagus and the normal lungs. The dose volume histogram analysis (DVH) has indicated a relation between the volume of the normal lung receiving doses in excess of 20 Gy and the risk of subsequent radiation induced pneumonitis. In the experience of Graham et al dealing with inoperable lung cancer, no case of grade 3 pneumonitis was seen when less than 25% of the lung received more than 20 Gy; this rate was 23% when the volume was greater than 40% [18]. In our own experience, the quality of the radiation procedure was a key factor. All patients treated after pneumonectomy between 1970 and 1985 were reviewed. Three groups were investigated: a control surgical group only operated on for an early stage I tumour, a group of patients treated with a three-field technique and a Co60 source, and a group of patients treated with a linear accelerator after treatment planning based on a postoperative CT. The dose delivered to the mediastinum was 56 Gy in daily fractions of 2 Gy. The 5-year survival rates were 4% for patients treated with Co60, and 30% for the surgical and the linac groups [19]. The latter groups included only stage III disease.

Postoperative irradiation of lung cancer is a very good model for 3D conformal radiotherapy. Schraube et al. have already shown that this technique made it possible to reduce the dose to the lung and the heart, while keeping the same total dose to the target area [20]. At the University of Giessen, 115 patients had a 3-D planned postoperative radiotherapy delivering a dose of 50 to 60 Gy whereas 437 patients had only surgical resection: the radiation course made it possible to reduce the risks of death in patients with

nodal metastases without increasing the risk of late damage [21]. Using a modern radiation technique, Mornex et al. were able to deliver doses between 50 and 55 Gy without impairing the patient lung functions [22].

The aim of postoperative irradiation is to increase survival by virtue of reducing the locoregional relapse risk; the pattern of failure analysis should help to select patients for such a treatment. Data from surgical series reported about 10% of local relapse for stage I disease *(Table 2*) [9,12,14,15,17,23-28]. In our own randomized trials, including only T1T2No tumour operated on by the same surgical team, the rates of «in field» local failures were 13% after surgery alone and 8% after postoperative irradiation respectively. Clearly, routine postoperative irradiation appears not to be indicated for stage I tumour after complete resection. In a recent trial including 104 patients with a pathological stage I non-small cell lung cancer, postoperative irradiation was restricted to the area of the bronchial resection and the hilum, and a dose of 50 Gy was delivered. This treatment reduced the number of locoregional relapse from: 1 out of 51 vs. 12 out 53 for surgery only [17]. The figure of 22.5% of local failure is very high as compared with many other surgical series. In contrast, local failure seems to be a more common problem in more advanced tumours, with failure figures ranging between 20 and 40%. In four large trials, a trend was observed for an improved local control after postoperative irradiation [12,13,14,16]. In the Lung Cancer Study Group trial, only one case of local failure was noted among 102 patients receiving postoperative irradiation in contrast to 21 out of 108 patients for the surgical arm only [13]. In the Feng trial, local failure within the chest dropped from 40% to 16% after postoperative irradiation for stage III disease [12]. In a review of controlled and retrospective studies of patients only those undergoing surgery or receiving additional postoperative irradiation for stage II and III disease, the rate of locoregional failure varied from 12 to 60% after surgery, and from 1 to 45% after postoperative radiotherapy (*Table 3*). The average local relapse rate was about 30% after surgery alone and 13% after postoperative radiotherapy [13,14,24,26,29-36]. Postoperative radiotherapy appears to improve local control but the survival benefit is not known.

Table 2. Pattern of failure after surgery for lung cancer.

Authors	Tumor Stage	Number of patients	Local failure (%)
Martini	T1-T2 N0	110	0
Immerman	T1-T2 N0	77	12
Van Houtte	T1-T2 N0	78	13
Pairolero	T1N0	170	6
	T2N0	158	6
Feld	T1N0	162	9
	T2N0	195	11
Granone	T1-T2 N0	53	22.5
Laffite	T2N0	70	14
Sawyer	T1-T2 N0	370	15
Lung Cancer Study Group	N1-N2	108	20
Stephens	T1-T2 N1	91	49
	T1-T2 N2	54	41
Feng	Stage II	82	29
	Stage III	80	37
Immerman	T1-T2 N1	22	41

At present, there is a general trend in favor of a neoadjuvant approach with chemotherapy, or a combined approach. This will raise a new series of questions: should postoperative irradiation be limited to incomplete resection for residual N2 disease, or should we decide about our treatment on the initial tumour extension? Several other questions remain unanswered: should the type of mediastinal resection be taken into account? What is the role of nodal capsular rupture, a well-known poor prognostic factor for head and neck cancers? What is the role of the histological type? In addition to the role of chest irradiation, brain failures present a common problem in many series questioning the role of prophylactic irradiation. However this issue has never been addressed in a well-conducted randomized trial.

Table 3. Local relapse after surgery with or without postoperative radiotherapy for locally advanced lung cancer.

	SURGERY		POSTOP. RADIOTH.	
Authors	**N**	**Loc. Rel. (%)**	**N**	**Loc. Rel. (%)**
Choi	32	53	41	31
Chung	29	48	38	8
Van Houtte			142	9
Emami			69	11
Lung Cancer Study Group	108	20	102	1
Ludwig Lung Cancer Study G.	253	30		
Immerman	22	41		
Durci	41	36	38	45
Herskovic			64	19
Astudillo	60	12	71	19
Baillet			203	34
Feng	162	33	134	13
Keller			242	13
Stephens	154	47	154	37

CONCLUSIONS

Surgery still remains the corner stone in the treatment of non-small cell lung cancer. The place of adjuvant treatment, either chemotherapy or radiotherapy, remains unclear. The possible benefits in terms of survival are probably very low, but due to the great number of patients suffering from this disease, this is a very important issue. Postoperative radiotherapy improves the locoregional control for stage III disease, but requires a very precise technique. More studies are still needed to answer many of the remaining questions.

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