Radiotherapy versus follow-up in the treatment of pathological stage Ia and Ib non-small cell lung cancer. Early stopped analysis of a randomized controlled study

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Abstract

Objective: This is an analysis of a randomized controlled clinical trial planned to evaluate the effects of adjuvant radiotherapy (AR) on the local recurrence rate in patients with non-small cell lung cancer (NSCLC) with pathological stage (pStage) Ia (pT1N0) and Ib (pT2N0). The effects of AR on the long-term survival have also been marginally evaluated.

Materials and methods: This clinical trial was planned with the hypothesis that AR on pStage Ia and Ib, R0 NSCLCs was effective on local recurrence rate. From July 1989 through March 1997, 104 patients with NSCLC who presented with pStage Ia and Ib have been observed and treated and entered the study. Male/female ratio was 91:13; the mean age was 62 years (range 41–75 years). All patients underwent major pulmonary resection and homolateral standard hilar and mediastinal lymph node dissection. pStage was T1N0 in 29 and T2N0 in 75 cases. Patients have been randomized ‘by chance’ into two groups (G1 and G2). G1 received radiotherapy, G2 did not receive any adjuvant treatment. Fifty-two patients entered G1 and 52 entered G2.

Results: Post-operative mortality was nil. Seven patients have been excluded from the study (four in G1 and three in G2), due to incomplete follow-up data. We do not report any radiotherapy-related complication or deterioration of lung function. The treatment effect on the local recurrence rate demonstrated a clearly significant protective effect of the AR. No statistically significant difference was found from the comparison of the 5-year survival rate of the treated (83%) versus untreated (70%) patients. No detrimental effect of the radiotherapy has been assessed.

Conclusions: AR in the treatment of pStage Ia and Ib NSCLC has been well tolerated and had a significant relative effect on the local recurrence rate but did not significantly modify overall survival even if a positive trend in the group of treated patients is reported.

Keywords: Non-small cell lung cancer; Early stage; Surgery; Adjuvant radiotherapy; Randomized study

1. Introduction

Surgery is regarded as the most effective method of controlling the primary tumour in non-small cell lung cancer (NSCLC) patients, provided a complete resection is possible and the risks of the procedures are low.

The 5-year survival rate after complete resection of patients with pathological stage (pStage) Ia (T1N0) and Ib (T2N0) is 67 and 57%, respectively [1]. In 1989, when the study we refer in this paper was planned, the cumulative 5-year survival value for pStage I disease was 63.5% [2].

Historically, many series have shown that approximately 20% of patients with resected, pStage I (Ia and Ib) NSCLC experience a cancer recurrence, either local (30%), distant (10%), or both (6%) [3–14]. Over the period of 5 years after initial treatment, overall cancer recurrence is 10% [13,15]. Furthermore, a certain number of patients (approximately 20%) with pStage I NSCLC dies within 5 years of cancer unrelated causes [13]. In 1989 we planned a controlled randomized clinical trial of adjuvant radiotherapy (AR) versus follow-up alone in pStage I NSCLC, with the rationale of evaluating the chance of killing any malignant cells remaining at the resection margins and, by this, to reduce local recurrence rate. Stage I NSCLC makes up approximately 30% of patients in most large series, and...
therefore any change in survival would affect more than 40,000 patients annually [16].

Despite the logical need for AR in an effort to improve local control and survival in the advanced stages of the disease, the role of such therapy in the management of pStage I (and II) remained a controversial issue [17–20].

On the basis of the recently reported conclusions of the Post Operative Radio-Therapy (PORT) Meta Analysis

Fig. 1. (A) Advanced two-dimensional and (B) three-dimensional treatment planning.
Trialists Group [21] that AR is detrimental to patients with early stage completely resected NSCLC and should not be used routinely for such patients, we carried out an analysis of our trial, to assess if our results were, at the moment, comparable and to ensure that it is still ethical to continue our clinical behaviour.

2. Materials and methods

2.1. Patient population and surgical considerations

From July 1989 through March 1997, 104 patients who presented with NSCLC and pStage Ia and Ib have been observed and, upon informed consent, entered the study given the following eligibility criteria: (a) pathological Stage Ia or Ib, R0, NSCLC; (b) age < 75 years; (c) absence of medical contraindications to major pulmonary surgery and radiotherapy (performance status ECOG 1); (d) agreement to carry out the whole protocol in our Institution.

The population was normally distributed: there were 91 men and 13 women, and the mean age was 62 years (range 41–75 years). Pre-operative evaluation and staging was accomplished, in all patients, by routine blood tests, standard chest X-ray, CT scan of the thorax, abdomen and brain, liver ultrasonography, whole-body bone scintigraphy, standard pulmonary function evaluation: global spirometry, KCO test (CO transfer corrected for alveolar volume), pulmonary perfusional scintigraphy, blood gases analysis. All of the patients underwent major pulmonary resection and homolateral systematic hilar and mediastinal lymph node dissection (a mean number of 20 lymph nodes have been dissected and examined). We performed 76 lobectomies, 17 bilobectomies and 11 pneumonectomies. Histology was confirmed to be Squamous cell carcinoma in 56 patients, adenocarcinoma in 38, large undifferentiated cell carcinoma in six and bronchiolo-alveolar carcinoma in four. The pStage was T1N0, R0 (Ia) in 29 cases and T2N0, R0 (Ib) in 75. The bronchial margin showed no tumour in all cases.

Patients, upon randomization, were divided into two groups (G1 and G2). G1 received radiotherapy 3–4 weeks after surgery with the following details: (a) technique: angled field, advanced two-dimensional (2D) and 3D supported; (b) fractionation: conventional (1 fraction per day); (c) daily fraction dose: 180 cGy; (d) total dose: 5040 cGy; (e) scheduled treatment duration: 4 weeks; (f) target volume areas: bronchial margin, hylum; (g) average target volume area: < 50 cm²; (h) radiation energy source: linear accelerator (Figs. 1 and 2). G2 did not receive any adjuvant treatment. At the moment of this analysis 52 patients have entered G1 and 52 G2. Respiratory function has been re-assessed 1 and 6 months after the completion of treatment (Table 1). This study has been evaluated and approved by the local Ethical Committee.
sample size has been considered inadequate for the evaluation of the effects of adjuvant radiotherapy on the long-term survival (where a number of 150–170 observations is needed). We planned this interim analysis, following the Pocock Group Sequential Design [23–25]. With a number of foreseen analyses \( (k) = 2 \) (one interim and one final), an \( \alpha \) error = 5\%, \( 1 - \beta = 80\% \) and the ‘shape parameter’ \( (\Delta) = 0.5 \), the nominal significance level \( (P) \) for our early stopping has been established to be 0.029. An ‘inflation factor’ related to the early stopped analysis of 15\% has been calculated and the sample size of the trial has been increased to 170–190 events. This value is to be reached to carry out the final analysis.

We evaluated the chances to carry out the analysis following the group sequential designs according to O’Brien and Fleming [26] and McPherson [27] but, with these methods, all interim analyses are carried out at extremely conservative significance levels, so the power to detect early differences is very low. From this point of view, the Pocock design we adopted is less conservative.

Endpoints of the analysis were the recurrence of lung cancer, either local either distant and, eventually, the lung cancer related death. Patients whose death was unrelated to lung cancer (14) were excluded from the evaluation of the survival differences between the two groups. The randomization has been realized ‘by chance’.

For the measurement of the treatment relative effect on the local recurrence rate a comparison of the disease-free intervals of the treated versus untreated patients calculated with the Kaplan–Meier method [28] has been realized and statistical significance has been assessed with the log-rank test. A similar procedure has been carried out to compare the survival curves. The analysis of the evolution of the respiratory function in time (1 and 6 months after completion of treatment) has been carried out according to the linear regression method.

3. Results

We observed two (2\%) major surgery-related complications. The first patient was diagnosed to have a broncho-

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<tr>
<td>FVC</td>
<td>+ 5.62</td>
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<td>( \Delta O_2 )</td>
<td>+ 5.12</td>
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<td>KCO</td>
<td>− 0.897</td>
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\(^a\) FVC, forced vital capacity; \( \Delta O_2 \) arterial-alveolar gradient; KCO, CO transfer corrected for alveolar volume. Mean values are corrected for height, age, basal values, type of surgery.

\(^b\) Not significant.

A significant treatment-positive effect on the local recurrence rate has been demonstrated \( (P = 0.023) \), as clearly demonstrated by the comparison of the disease-free interval curves (Fig. 3). The local recurrence rate in the \( G1 \) group was 2 (1/48) versus 22\% (10/49) in the \( G2 \) group. The distant recurrence rate was, respectively, 24 (10/48) and 24\% (12/49) for \( G1 \) and \( G2 \). No detrimental effect of the AR on the survival has been documented; furthermore, even if not significantly, a positive trend can be assessed in the treated vs. the untreated group in the 5-year survival rate (83 vs. 70\%; \( P \) not significant). The pathological stage proved to be the strongest prognostic factor, in fact the 5-year actuarial survival for the \( T1N0 \) group \( (G1 + G2) \) was 87\% vs. 63\% of the \( T2N0 \) group \( (G1 + G2) \) with \( P = 0.009 \); thus the significant difference among pStage Ia and Ib has been confirmed in our experience, too.

4. Discussion

Stage I (Ia and Ib) NSCLC represents early cancer and is best treated by surgery, whenever possible. Despite the expectation of long-term survival after resec-

![Fig. 3. Kaplan–Meier analysis of the disease-free intervals: treated vs. untreated.](https://academic.oup.com/ejcts/article/18/4/418/420708)
tion without adjuvant therapy, recurrence or new cancers develop in a third of patients, whereas local recurrence rate, distant and both rank, respectively, 30, 10 and 6% [3–14]. The standard surgical treatment of localized stage I NSCLC is lobectomy [12–14,29,30] with mediastinal lymph node dissection, a procedure that, even if not always considered prognostically significant [31,32], should be routinely performed regardless of the extent of pulmonary resection to stage the disease accurately by assessing the status of lymphatic neoplastic involvement [13,15,30].

However, when dealing with a ‘potentially curable’ disease, as the stage I NSCLC is considered to be, the limited performance of a ‘radical’ operation alone in this setting accounted for the rationale of the many tries at improvement by adjuvant therapy. On this occasion, we will discuss adjuvant radiotherapy (AR).

Post-operative irradiation is usually administered after resection of cancer whose pStage shows a N1 or N2 involvement or when resection is incomplete or when the cancer was adherent to adjacent structures (T3, T4). AR has been investigationally used after resection of N0 diseases in some clinical trials [17–20] (with only the trials of Refs. [17] and [18] carried out in a randomized controlled fashion) with the result that the role of AR in the treatment of early stage NSCLC remained unclear, with a generalized detected detrimental effect on survival.

As stated, in 1989 we planned a randomized clinical trial of AR versus follow-up in the treatment of pathological Stage I NSCLC. We were carrying out our study according to the planned guidelines when a systematic review of all the available randomized evidence and the combination of the results of the published and unpublished trials in a meta-analysis of individual patient data has been reported by the PORT Meta-Analysis Trialists Group [21]. Following the interpretation of the results the authors concluded that AR is detrimental to patients with early stage completely resected NSCLC and should not be used routinely for such patients. Therefore, we planned an early stopped analysis of our trial to answer the crucial questions:

- Were our materials and methods and results comparable with those used in that meta-analysis?
- Does AR increases mortality in patients operated on for lung cancer with a pathological early stage?
- Was it ethical to go on with our trial? Is there any space left for AR in the pStage I (1a and 1b) NSCLC?

Radiotherapy is ‘a subtle and complex business and several factors need to be considered: technique, beam energy, volume of tissue irradiated, total dose, dose per fraction, interval between fractions, overall treatment time’ (Munro, 1998) [33].

The importance of performance status, total dose and treated volume, when dealing with lung radiotherapy has been well established, particularly in patients with medically inoperable or unresectable NSCLC treated with radiation therapy alone.

In fact, it is a dictum of radiation therapy that the risk of functionally significant radiation pulmonary toxicity is essentially proportional to the volume of irradiated lung, at least beyond a minimum dose of 18–20 Gy [34,35]. In this setting, the risk of radiation pneumonia should remain below 5% for the whole lung irradiation to these doses while smaller volumes of irradiated lung will generally show radiation pneumonia above 25 Gy [36]. Although much less has been written regarding the likely relationship of irradiated lung volume to pulmonary toxicity, there is little objective clinical data evaluating this effect, especially as it relates to extent of coverage of treated lung parenchyma. These data suggest that an increased lung toxicity group up to field sizes of 180 cm² [34,37]. As described, in our protocol the maximum volume of irradiated lung is by far less than 180 cm² (50 cm²).

As reported in Table 2 the PORT studies included patients treated on 60Co units: such units are no longer acceptable for the treatment of lung cancer patients. In fact, in one non-randomised study of AR, 5-year survival for patients treated on a 60Co unit was 8% compared with 30% for patients treated on a linear accelerator [19]. In this setting, according to Munro [33], we do believe that data obtained from obsolete equipment cannot be directly relevant to contemporary practice. Moreover, the details of radiotherapeutic technique and dose need to be scrutinised: although there is no evidence that the results reported in the PORT meta analysis [21] were influenced by radiotherapy dose and therefore no indication that any one of the individual schedules used was any less detrimental than others, indeed there is still scope for investigation of more modern radiotherapy to further assess the value of technique, beam energy, total dose, dose per fraction, interval between fractions and overall treatment time.

In this view, our materials and methods are not completely comparable with those reported in the PORT meta-
analysis, and the evaluation and assessment of the results of such a different type of AR, as the one we used, if compared with those evaluated in the PORT analysis, should be absolutely free and independently considered from the bias represented by the PORT Group conclusions that confounds the expectations of years and years of adjuvant treatment with radiotherapy in early stage NSCLC.

Our results (Fig. 3) are comparable in terms of evaluation of local recurrence rate (in our study AR was clearly a protective factor) and long-term survival where we do not report any detrimental effect of AR on survival, even if our results are not statistically significant.

In the PORT study, the excess mortality in the irradiated group is noticeable from about the fourth month from randomization and increases over the subsequent 8 months (range 4–12 months). This process, is, in the words of the authors, radiation induced, and clearly connected with the course of a radiation pneumonitis [33]. The rate of treatment-related deaths was doubled in patients treated with radiotherapy (P = 0.04), and the intercurrent deaths was 15% with AR and 9% with surgery alone (P = 0.003). Due to the fact that radiation pneumonitis could very easily mimic broncho-pneumonia, the treatment-related deaths may be ‘misconstructed as intercurrent’ (Munro) [33]. Moreover, in our experience, we do not report any treatment related death (no patient developed lethal broncho-pneumonia during the observation). Functional results, in fact, clearly demonstrated that there was not any deterioration in the lung function, even if a significant flattening in the increase slope of FVC in the treated group was detected and very probably correlated with the treatment (Table 1). This evidence is, in our opinion, very probably due to the small amount of lung parenchyma that is effectively irradiated in our protocol.

On the basis of the results we report we can conclude that:

- patients with pStage Ia and Ib who underwent AR demonstrated a significant decrease in the local recurrence rate and did not show any treatment-related mortality or significant morbidity;
- at the moment, the 5-year actuarial survival rate of the treated patients does not suffer any detrimental effect from the AR treatment; and
- the chapter of AR in early stage NSCLC is not closed and, in this setting of disease, more trials of modern AR are required.

However, through the PORT overview we received a very valuable lesson to be incorporated in the planning and evaluation of the results of novel schedules of AR in the early stage of NSCLC.

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References


Appendix A. Conference discussion

Dr P. Van Schil (Edegem, Belgium): What precise definition did you use for local recurrence? And how did you differentiate it from, for example, a second primary lung cancer or an ipsilateral lung metastasis?

Dr Margaritora: We obtained cytological/histological confirmation of all recurrences. Then all patients were operated on in our institutions, and our pathologists confirmed that they had recurrences of the primary tumor and a second primary. Pre-operative diagnosis and post-operative examination of the specimen were the only criteria for us and our pathologists to define as recurrence the cases we reported in this presentation.

Dr J. Hutter (Salzburg, Austria): Did the grading have any influence on the local recurrence in this group, the grading of the tumor?

Dr Margaritora: No, in this study we did not consider the grading of the tumors. Maybe in the future we will do it for the final analysis of our experience.

Dr G. Massard (Strasbourg, France): If we look at your results, you bring us striking information. We learned last summer that radiotherapy is detrimental, and now you show us that it is beneficial. So I would just like to know whether there might be a selection bias in your series. You have included 100 patients over a 10-year period, and I anticipate that you have operated on many more patients during the period. So what is the percentage of the Stage I patients actually operated in your department included in this study? Otherwise said, during the duration of the study how many Stage I patients did you operate on at your department and how many did you include in the study?

Dr Margaritora: Regarding the first part of your question I would like to underline that there are some very important differences between the port studies and ours and that, in our opinion, lead us to our different results, as I explained in my presentation. In our institution, our statisticians dictated us very strict eligibility criteria, and so in this study we included only patients who satisfied them. For example, we excluded all patients in which mediastinal lymph node dissection was not complete and a number of at least 20 lymph nodes were obtained. Unfortunately, this is a mono-institutional trial. So the number of selected patients in the first years of our experience was very low. Now, in the last 2 years, we are selecting more than 25 patients per year. So I hope that in the next year we will close the trial and we will be able to obtain more definitive conclusions.

Dr W. Klepetko (Vienna, Austria): Could you elaborate a little bit more about your follow-up protocol? Were all these patients regularly followed by CT or other investigations, or did you diagnose local recurrence only in cases where patients became symptomatic?

Dr Margaritora: No. In Italy we are currently doing an intensive follow-up. This means that every 6 months we perform a complete restaging, by total body CT scan, bone scan and liver ultrasound, for the first 3 years and yearly for the following period.
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