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Controversies in the Treatment of Non-small Cell Lung Cancer

Anna Gregor

INTRODUCTION

NON-SMALL cell lung cancer (NSCLC) represents about three-quarters of all the lung cancer histologies. In the UK it accounts for 30 000 annual deaths. This high incidence places lung cancer in the forefront of diseases with a major public health impact. The overall prognosis of patients with NSCLC is poor, with less than 10% surviving 5 years. In the epidemiological perspective treatment makes a small impact on overall survival [1].

These incidence and survival figures hide a variety of clinico-pathological scenarios with widely differing probabilities of occurrence and outcome. Whilst it is easy to become nihilistic and dismissive of treatment impact as well as less enthusiastic about research, the frequency of lung cancer makes even a trivial improvement in treatment-related outcome a worthwhile achievement. In parallel, a futile aggressive approach to therapy will lead to over-treatment on a massive scale with resultant unjustifiable costs both in patients' toxicity and medical budgets. In this context optimisation of treatment strategies continues to generate a lively debate about the merits of individual options. Discussions are spread throughout the clinico-pathological spectrum but can be conveniently grouped into areas based on simple patient and tumour-related parameters.

In patients with resectable tumours, discussion involves "minimal staging", extent of surgical resection and the role of post-operative adjuvant treatment. The potential of curative radiotherapy as an alternative to surgical resection for certain patients' groups has recently been re-examined and will no doubt provide a source of most interesting debate in the future.

The management of the fit patient, with locally advanced tumour and no evidence of metastases, provides most of the present controversies. Proponents of aggressive treatment will argue the merits of "induction" or "neo-adjuvant" therapy, combinations of chemotherapy and irradiation, or high dose radiotherapy alone. The therapeutic nihilists remain unconvinced by available data and advocate minimal treatment concentrating on quality of life, or purely experimental therapy.

In more than half of presenting patients, consideration of local control is irrelevant and treatment must address the control of systemic disease. There is general agreement on the requirements for supportive care but considerable debate on the optimal way of achieving it. Both the role and schedules of radiotherapy are under evaluation, as is the contribution of chemotherapy to the quality of life of these patients.

Technical optimisation of planning and delivery of thoracic radiotherapy is agreed and widely accepted. The research activity centres around multiple daily fractions, accelerated fractionation and other unconventional schedules. Early dose-finding studies have identified several problems, including altered toxicity profiles and major methodological drawbacks in assessment of local control. The difficulties are further compounded by the minor impact that improved local control will provide; hence large numbers of patients will be required for randomised studies to be meaningful.

PRETREATMENT STAGING

The aim of pretreatment staging is to ensure appropriate therapy for an individual patient. In the case of lung cancer this means selecting patients likely to benefit from surgical resection. The process depends on the extent of the tumour, general fitness of the patient and the general availability of diagnostic and treatment-related expertise.

The most important prognostic factor is mediastinal node involvement [2]. It correlates well with resectability and predicts survival. Chest X-rays are notoriously insensitive in detecting mediastinal nodal involvement. Computed tomography (CT) is much more sensitive but it shares, with other radiological investigations, lack of specificity [3]. Where CT suggests mediastinal invasion and/or nodal spread, mediastinal exploration using mediastinoscopy or mediastinotomy is vital for confirmation. Involvement precluding resection will be found in half of such patients [4].

For most surgeons mediastinoscopy remains the gold standard for resectability. In the rare patient with single ipsilateral intracapsular deposits only Pearson reported a resectability rate of 85%. For those patients the 5-year survival with post-operative radiotherapy was 18%. Overall the 5-year survival was 9% which was appreciably lower than the operative mortality of 16% [5]. Martini and his colleagues [6] have prospectively demonstrated the relationship between resectability, survival and site and extent of mediastinal involvement. The use of systematic intra-operative mediastinal node dissection has demonstrated unsuspected involvement in 25% of cases [7]. This is now becoming a surgical staging requirement. Without a reliable assessment of mediastinal nodal status we cannot rationally discuss prognosis with individual patients, choose suitable postoperative adjuvant strategies or assess their results.

POSTOPERATIVE RADIOTHERAPY

Postoperative radiotherapy for completely resected patients with nodal involvement significantly reduced local recurrence rate in a study by the Lung Cancer Study Group [8]. Unfortunately this study, together with the four other randomised trials summarised in Table 1, have failed to produce an improvement in survival. There are a number of reasons which could explain this disappointing finding. The early studies [9, 10] can be criticised for sub-optimal radiation dose and treatment volumes. In the study of Van Houtte *et al.* [11], radiation toxicity may have acounted for a large proportion of the early deaths in the radiotherapy treated arm. The study from the former lung group of the EORTC reported by Israel [12] as an interim analysis had

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Table 1. Postoperative Radiotherapy NSCLC

No. of patients	TNM	Radiotherapy (Gy)*	Histology	Results	Ref.
202	NO	45 (20)	All	NS	9
73	NO/N_1	45 (25)	All	NS	10
224	NO	60 (30)	All	NS	11
392	NO-2	45 (20)	Squamous	Local relapse	12
230	N_1-2	50 (25)	Squamous	Local relapse	8

*Number of fractions in parentheses.
NS = not significant.

a complicated design with randomised post-operative radiotherapy (45 Gy in $4\frac{1}{2}$ weeks) and chemotherapy with or without immunotherapy. The mature data from this study is not available. Local relapse is an important site of failure in patients with N1 disease (Table 2) and can represent up to half of total failures in completely resected stage I NSCLC [13–19]. In contrast, in patients with advanced nodal disease, systemic relapse becomes the predominant pattern of failure. It is for this reason that the EORTC lung cancer group together with the GETCB are conducting a randomised trial in completely resected and carefully intra-operatively staged patients with pTN1 or minimal N2 disease using optimal radiotherapy volumes, doses and techniques. This trial, which requires a close collaboration between surgical and radiotherapy expertise, is experiencing recruitment difficulties but is an important study without which further recommendations about the role of adjuvant radiotherapy in this group of resected patients cannot be made.

ADJUVANT CHEMOTHERAPY

Considerable effort has been expended testing the role of chemotherapy as a surgical adjuvant. The early studies [20–24] were negative. These results are frequently blamed on suboptimal chemotherapy. The Lung Cancer Study Group (LCSG) studies with platinum containing combinations [25] have shown a small (8–12 months) benefit in disease-free and overall survival. However, these studies share the drawback of not having a control group. In the first trial cyclophosphamide/doxorubicin/-cisplatin (CAP) was compared to intra-pleural BCG in completely resected stage II or III adenocarcinomas. In the second study all histological groups with evidence of proximal nodal involvement at surgery were given post-operative irradiation. A significant improvement in early disease free survival (40 vs. 25%) was seen in the group receiving additional CAP. The greatest impact was seen in patients with non-squamous histology. In patients with completely resected T2N1 and T2N0 NSCLC four courses of postoperative CAP showed no benefit.

Table 2. Patterns of failure after resection stage I NSCLC

No. of patients	% Local relapse	% Metastases	Reference
77	12	27	13
110	0	18	14
846	18	16	15
36	22	5	16
358	10	24	17
328	6	29	18
97	19	21	19

Table 3. Randomised trials of thoracic radiotherapy and chemotherapy in inoperable NSCLC

No. of patients	RT(64)	RT plus CT	Response rate	MST	2-yr survival (%)	Ref.
62	60	–	40	8.5	–	
68	60	VBL+P	57	16.5	–	29
119	55	–	44	10.3	20	
119	55	CAP	49	11.0	20	30
55	60	–	64	9.7	12	
54	60	MACC	52	10.6	23	31
38	50–60	–	19	9.3	6	
35	50–60	ACNU	89	11.3	19	32
310	0	DVS	10	10.2	9	
	60	–	30	9.6	12.5	
	60	DVS	34	11.2	13	33
62	45	–	57	11.7	–	
49	45	CAMP	39	10.0	–	34
177	65	–	20(CR)	–	14	
179	65	VCPC	16(CR)	–	21	35

RT = radiotherapy, CT = chemotherapy, CR = complete response, MST = median survival time. VBL = vinblastine, P = cisplatin, ACNU = nimustine, DVS = vindesine, CAMP = cyclophosphamide/doxorubicin/mitomycin/cisplatin, VCPC = vindesine/cyclophosphamide/cisplatin/lomustine.

RADICAL RADIOTHERAPY

A number of small single institution studies using high-dose radiotherapy [26–28] have reported impressive 5-year survival rates in clinically staged patients with "early" lung cancer. Whether the 35–50% 5-year survival reported can be sustained if a larger number of patients were treated is unknown. These reports show that long-term survival after radical radiotherapy is a possibility and that a realistic alternative to surgical resection can be provided for groups of patients where high surgical mortality is an accepted hazard. A full assessment will be hampered by problems of patient selection and difficulties in finding comparable levels of assessment of nodal status.

COMBINED MODALITY TREATMENT

There are two main controversies concerning the treatment of unresectable but fit patients with no clinical evidence of extrathoracic metastases. The first concerns the role of chemotherapy as a primary cytoreductive treatment designed to improve subsequent local regional control and reduce metastatic rate. Various terms have been used to define the initial use of chemotherapy (neo-adjuvant, induction, protoadjuvant and combined modality treatments) and have all been adding to the general confusion of terminology and purpose.

The role of combined modality therapy has been addressed in seven recent randomised trials (Table 3). Only one of these studies reported a survival advantage [29]. The interim analysis of the first 130 evaluable patients in this Cancer and Leukemia Group B (CALGB) trial showed improved overall response rate (40% vs. 57%) and median survival time (8.5 vs. 16.5 months) for the radiotherapy vs. radiotherapy and chemotherapy group respectively. The log rank analysis of the survival curves confirmed a significant difference and the trial was stopped. The confirmation of this finding is awaited from an ongoing intergroup trial of ECOG and RTOG and needs to be viewed together

Table 4. "Neoadjuvant" therapy in IIIA NSCLC

Regimen	No. of patients resected/ total	Operative mortality (%)	MST (x/12)	Ref.
MVP	28/41 (68)	3.5	19	36
CAP + RT	19/39 (49)	0	12	37
5-FU + DDP + RT	62/130 (47.6)	5	14	38
5-FU + DDP + RT	46/84 (54)	0	10.5	39
MVP	22/39 (59)	9.2	19	40

MVP = mitomycin/etoposide/cisplatin, 5-FU = 5-fluorouracil.

with the six other randomised trials failing to show overall survival benefit for multi-modality therapy.

In the absence of clear advantage for combined modality therapy and no studies with a true control arm we must continue to question the role of high dose irradiation in this subset of patients when compared to short and undemanding regimens designed for symptom control.

The question was addressed to an extent by Johnson *et al.* [33] when vindesine was used as a control in one arm of a randomised trial which failed to show significant survival difference. Treatment on progression however was not standardised and many of these patients received high dose radiotherapy later. It may be necessary to await development of more effective chemotherapeutic regimens before submitting more patients to the rigours of phase III trials. All these clinical investigations must contain prospective assessment of quality of life which may influence the interpretation of small survival gains using treatments with well defined costs and toxicities.

A number of phase II studies of "neo-adjuvant" therapy in "marginally" operable patients have been reported (Table 4). Resectability rates of around 50% can be achieved without significantly increased morbidity. A variety of chemotherapy and irradiation schedules have been used [36–40]. About 30% of resected specimens are free from pathologically viable tumour.

In the absence of appropriate controls the contribution of these exciting findings to survival cannot be assessed and we must not forget that preoperative radiotherapy alone is capable of tumour sterilisation [40].

The recent IASLC-sponsored workshop recommends that value of induction therapy needs to be tested prospectively in controlled studies and should not be considered as a standard treatment.

Separate studies need to be designed: (a) for patients in whom immediate surgery can be attempted (T1-T3N1 and minimal N2); (b) for patients for whom attempted surgical resection may be done if sufficient tumour regression is obtained (T1-3 non-minimal N2); and (c) for those patients in whom attempted surgical resection would not be appropriate even if induction therapy is effective (IIIB and N2 disease with local mediastinal invasion).

Randomised comparisons should be provided against standard therapy for each separate group. The principal end point should be survival, with toxicity and quality of life as secondary objectives. Surgical and pathological findings at thoracotomy, relapse and response rate all provide interesting data but the difficulties with comparative and reliable assessment of many of these features and the unpredictable relationship between "regression" and "relapse" make these unreliable.

HYPERFRACTIONATION RADIATION THERAPY

Irradiation treatment schedules have been the subject of assessment of unconventional fractionation since the late 1950s [42]. The initial advantage of split course radiation was better patient tolerance, the rest period allowing for repair of normal radiation damage. Later came the realisation that tumour repopulation may outweigh any possible advantage of improved patient tolerance. The practical advantage of filtering out the 30–70% of patients not completing the split course due to tumour progression should be replaced by better pretreatment assessment. No convincing difference in terms of response or survival has been found in the majority of randomised trials testing this concept [43–46]. There is a significant theoretical disadvantage of high fraction size and a number of studies have shown variable but fast doubling time with *in vivo* estimates of potential doubling time of 6–9 days [47]. The normal tissue tolerance in the thorax is highly dependent on fraction size. That no excess of late radiation damage was seen in these studies may reflect the poor overall survival of the population rather than true absence of clinically detectable problems [48]. A small but important post-mortem study [49] observed better tumour sterilisation (53% vs. 13% for small tumours and 29% vs. 18% for large tumours) when small fractions were compared to large ones.

Based on the evidence of fast potential doubling time and tumour repopulation a regime of continuous hyperfractionated accelerated radiotherapy (CHART) has been developed by Saunders and Dische [47]. The pilot study has demonstrated an impressive 42% CR rate and 40% 2-year survival in locally advanced tumours with 3 daily fractions of 1.5 Gy to a total dose of 54 Gy in 12 days. An expected and predictable increase in early radiation reactions is seen. However, two unexpected cases of radiation myelitis have recently been reported, at a dose which is conventionally considered safe [50]. This important clinical concept based on sound scientific principles is now being tested in a randomised trial.

Cox *et al.* recently reported [51] a trial of hyperfractionated radiation therapy where two fractions of 1.2 Gy were given each day. Patients were randomly assigned to one of five total doses ranging from 60 Gy in 5 weeks to 79.2 Gy in 6½ weeks. An advantage from higher total doses was found in a retrospectively analysed subset of patients with good performance status and minimal weight loss. Based on these results a hyperfractionated arm has been added to the RTOG and ECOC collaborative study comparing conventional radiotherapy alone, hyperfractionated radiotherapy and standard radiation preceded by induction chemotherapy.

SYMPTOM CONTROL

Symptom control is an important priority for the vast majority of patients with lung cancer. How best this can be achieved has been investigated in a number of settings. Chemotherapy does not produce sufficient response rates to outweigh its toxicity and its use in patients with metastatic lung cancer should be confined to experimental protocols. Radiotherapy provides effective relief for the majority of patients with symptoms related to local tumour or metastases. Radiotherapy schedules vary considerably, from single fractions to protracted courses of irradiation over 4–6 weeks. Recently the Lung Cancer Working Party (LCWP) of the Medical Research Council (MRC) performed two trials comparing symptom control and quality of life in patients treated with various schedules of palliative radiotherapy. In the first one, 30 Gy in 10 daily fractions was

compared with 17 Gy in 2 fractions one week apart. In 374 patients they were equivalent in symptom control, toxicity and median duration of palliation. As one would expect in a group of advanced disease patients, there was no survival difference [52].

The LCWP's subsequent trial compared the two fraction regimen with a single fraction regimen of 10 Gy. Analysis of this study is in progress. These studies indicate that undemanding and non-toxic treatment can provide effective symptom control.

CONCLUSION

The frequency of lung cancer incidence and limited treatment options make it imperative that we adopt optimal management strategies for the majority of patients. To achieve this aim we must resolve some of the existing controversies and search for new and more effective ways of dealing with this common and mainly incurable disease.

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Lung Cancer Biology

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INTRODUCTION

IN SPITE of major advances in our understanding of the prognostic factors of patients with lung cancer, little advance has been made in improvement in the overall survival of patients with this disease over the past decade. In the USA it has been anticipated that this year there will be almost 160 000 new cases of lung cancer, and the vast majority of these patients will die from their disease. The 5 year survival rate for all patients with lung cancer remains between 7 and 10%. For patients with non-small cell lung cancer (NSCLC) the only hope for many for prolonged survival is directly related to the resectability of this tumour. In contrast, for patients with small cell lung cancer (SCLC), which accounts for 25% of all new cases of lung cancer, the sensitivity of this type to chemotherapy and/or radiation therapy predicts well for the survival of patients with this disease. However the vast majority of patients with SCLC will have widespread metastatic disease at the time of initial presentation and even with intensive cytotoxic chemotherapy less than 10% of all patients will be cured of their disease. While many factors may influence the overall survival of patients with lung cancer, including performance status and stage of disease, it is now clear that biological factors inherent within the tumour cells themselves may be of clinical importance. These properties include the expression of neuroendocrine markers and the expression of drug or radiation resistant genes or oncogenes coding for more malignant behaviour or specific cytogenetic abnormalities. Here we will review the recently recognised biological properties of lung cancer cells and discuss their application in the management of patients with this disease.

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CELL LINES OF LUNG CANCER

The ability to establish permanent cell lines of both SCLC and NSCLC has greatly enhanced our understanding of the biological properties of these tumour cell types. The development of specifically designed serum-free hormone supplemented medium for the selective growth of both SCLC and NSCLC has provided us with large panels of cell lines to study biological properties [1–6]. SCLC cell lines grow as floating aggregates of tightly to loosely packed cells, while NSCLC grow usually as adherent monolayer cultures. Both cell types form tumours in soft agarose and are tumorigenic in nude mice. Based on their expression of a variety of biochemical markers including L-dopa decarboxylase (DDC), neuron specific enolase (NSE), creatine kinase-BB (CK-BB) and gastrin-releasing peptide (GRP) SCLC cell lines can be subtyped into two major categories, namely, classic cell lines which express high levels of all four of these markers, and variant cell lines which have selective loss in their expression of both DDC and GRP. In addition classic cell lines have a more aggressive growth behaviour *in vitro*, a higher colony forming efficiency in soft agarose and when implanted into athymic nude mice have a shorter latent period to tumour formation.

Recently it has been clearly demonstrated that up to 30% of cell lines or fresh tissue obtained from patients with NSCLC will have features of neuroendocrine differentiation, in particular the expression of high levels of DDC and NSE. Thus it can be observed that both within SCLC and NSCLC two major divisions of cell types can be identified, i.e. those that have evidence of neuroendocrine differentiation and those that lack it. The expression of these neuroendocrine markers may be important