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Surgery for nonsmall cell lung cancer: can improvements be made?

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Surgery for nonsmall cell lung cancer: can improvements be made? S.G. Spiro. ©ERS Journals Ltd 2003.

ABSTRACT: Low-dose spiral computed tomography (CT) for the earlier detection of lung cancer is at the stage of producing hypothesis-generating studies. These studies have shown that more cancers are found at a favourable stage (IA) in prevalence screening but that the fewer numbers found in incidence screening tend to have a slightly worse stage. Randomised controlled trials will be necessary to resolve the place of spiral CT screening.

The role of neo-adjuvant chemotherapy before surgery in nonsmall cell lung cancer looks less promising than suggested by earlier studies and the place of adjuvant chemotherapy following surgery appears to be unhelpful, although results of some large, randomised international studies are still awaited.

Radical radiotherapy is a poor alternative to surgery in resectable patients who refuse or are unfit for surgery and postoperative radiotherapy is detrimental. Positron emission tomography scanning offers a genuine opportunity to identify occult disease and improve staging prior to surgery and therefore save futile thoracotomies in ~20% of patients otherwise apparently suitable for resection.

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The hypothesis-generating studies using low-dose spiral computed tomography (CT) scanning in volunteer populations, particularly in the USA and Japan, have shown an up to four-fold increase in the prevalence pick-up of small nodules, usually not seen on a chest radiography, that ultimately have turned out to be malignant. These malignant small nodules are not alone and the same pilot screening studies have also picked up a large associated incidence of benign nodules on the screening scan. Much work needs to be carried out, particularly using the randomised controlled trial as the main instrument, to determine the true incidence of prevalence and annual (or regular incidence) cancers picked up by screening, and to unravel the detection of these tumours from the often plentiful benign nodules also found on these scans. Early indications, primarily based on work in the USA, suggest that the incidence of benign nodules is up to 13%. This would indicate that volunteers having regular annual scans would be found to have a nodule every 5–6 yrs [1]. Despite the complexity of determining the place of spiral CT, it is to be hoped that it will have an effect on lung cancer mortality. It is only mortality that will have a bearing in screening studies, as the randomised controlled trials have to overcome the inherent statistical difficulties of lead time bias, length time bias and overdiagnosis bias. Similarly, the spiral CT is adept at identifying peripheral nodules, but is of no value or very little value at identifying cancers that originate from the central airways. The role of spiral CT as a future screening tool has still to be decided and this will not be possible until its screening value has been assessed in other parts of the world where the peripheral adenocarcinoma is less common than in the USA and Japan (*e.g.* Europe).

Surgical removal remains the conventional approach to lung cancer, wherever possible. The TNM (primary tumour, regional nodes, metastasis) staging classification was modified in 1997 by MOUNTAIN [2] and it highlights the importance of stage at presentation to prognosis. The most important stage classification in relation to screening studies is stage IA, which comprises a peripheral solitary nodule <3 cm in diameter. Although the 5-yr survival for this presentation is 67% it comprises <10% of all lung cancers and yet this is the stage of presentation that the peripheral nodule found on CT screening predominates. Whilst a review of the staging cascade shows that stage is related to prognosis, it is not perhaps so clear cut. The study by PATZ *et al.* [3], who reviewed a large series of stage IA (T1N0M0) lung cancers in 510 patients over 19 yrs, showed that there was no effect of tumour size on survival. This, they would argue, is due to the inherent biological properties of the cancer, which will have had ~20–30 volume doubling times of growth until it reached detection. During this period of time there would have been much opportunity to seed metastases and, therefore, tumour size itself may only be a factor in prognosis and the inherent biological aggression of the cancer itself should also be a very important factor. The staging classifications and cumulative 5-yr survival after treatment based on the pathological stage found at assessment (usually surgery) are shown

Table 1. – Cumulative 5-yr survival after treatment based on pathological stage found at assessment

Stage/TNM	Subjects	Subjects surviving cumulative %		
		1 yr after treatment	3 yrs after treatment	5 yrs after treatment
IA				
T1N0M0	511	91	71	67
IB				
T2N0M0	549	94	67	57
IIA				
T1N1M0	76	88	65	55
IIB	375	77	47	39
T2N1M0	288	78	47	39
T3N0M0	87	76	47	38
IIIA	399	64	32	23
T3N1M0	55	65	30	25
T1-2-3N2M0	344	64	32	23

TNM: primary tumour, regional nodes, metastasis staging. Modified from [2].

in tables 1 and 2. It is clear that the higher the stage, the better the patient's prognosis.

Considerable effort has been made to assess whether the addition of chemotherapy and/or radiotherapy both prior to (neo-adjuvant) or following (adjuvant) surgery can make an impact on survival. It is still not clear whether neo-adjuvant treatment can improve surgical 5-yr survival, although useful information has recently become available. The question as to whether adjuvant therapy can improve survival is also becoming clearer.

Neo-adjuvant chemotherapy

The main issue is whether neo-adjuvant chemotherapy improves survival in conventionally resectable patients, *i.e.* those with stage I or stage II disease (T1, 2 or 3 N0; T1, 2 or 3 N1) and also those with stage IIIA unforeseen N2 involvement found on pathological examination to contain microscopic disease. The second issue is whether chemotherapy can debulk and downstage more advanced disease, *i.e.* in patients who have bulky, abnormally sized ipsilateral mediastinal lymph nodes found on CT scanning that are ultimately biopsied and shown to contain tumour. These are lymph nodes >1 cm in diameter in their short axis and would normally be regarded as implying unresectability. These patients would not normally be considered for surgery and would be treated by radical radiotherapy or chemotherapy-irradiation. However, if chemotherapy was truly effective, surgery might be possible if chemotherapy could downstage these patients and make them operable. It is more probable that this merely reduces the bulk of the abnormal nodes but does not "sterilise" them.

Table 2. – Stage grouping and TNM (primary tumour, regional nodes, metastasis) staging subset

Stage	TNM Subset
Stage 0	Carcinoma *in situ*
Stage IA	T1N0M0
Stage IB	T2N0M0
Stage IIA	T1N1M0
Stage IIB	T2N1M0
	T3N0M0
Stage IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
Stage IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
Stage IV	any T any N M1

Reproduced with permission from [2].

There are only three important randomised controlled-phase III studies that have assessed the role of neo-adjuvant chemotherapy in resectable patients *versus* surgery alone. Most of the data for neo-adjuvant chemotherapy have come from phase II trials, often where the numbers are small and the studies have not always been straightforward, *i.e.* some have used chemotherapy alone prior to surgery and others chemotherapy and irradiation. The phase II studies of chemotherapy followed by surgery have shown considerable activity. Response rates to chemotherapy range from 50–78%. The overall peri-operative mortality ranges from 0–17%, figures which extend well beyond the normal 5–8% peri-operative mortality for lobectomy and pneumonectomy in patients who have not had prior treatment. The median survival in these phase II studies has ranged from 12–20 months and ~20–30% of all these resected patients have had a subsequent local relapse [4–8].

In 1994, two small randomised controlled trials were published looking at the role of neo-adjuvant chemotherapy *versus* surgery alone in stage IIIA nonsmall cell lung cancer (NSCLC). There were 60 patients in each study [9–12]. These studies closed early because of a disparity in survival between the two arms in favour of neo-adjuvant chemotherapy. The studies showed marked survival differences; in the study of ROSELL and co-workers [11, 12] no 5-yr survivors were found following surgery, although there was a 17% 5-yr survival rate following neo-adjuvant chemotherapy and surgery. The American study of ROTH and co-workers [9, 10] found a 15% 5-yr survival rate following surgery and a 36% survival rate following neo-adjuvant chemotherapy. However, the surgery arm faired particularly badly in the study of ROSELL and co-workers [11, 12] and there were disparities between tumour K-ras mutation and deoxyribonucleic acid aneuploidy in the two groups which, in some studies, have been shown to be indicators of poor prognosis. These studies have made a strong case for the value of neo-adjuvant chemotherapy.

Earlier this year, a much larger French study was published [13]. This study included 355 patients of

stage I (except T1N0), stage II and stage IIIA NSCLC. Patients received primary surgery or two courses of mitomycin, ifosfamide and cisplatin combination chemotherapy followed by surgery. The patients who responded to chemotherapy had a further two courses of chemotherapy postoperatively. Any patients who were pathologically staged to have T3 or N2 disease in either arm then received thoracic radiotherapy. The response to treatment was high, in that 64% of patients in the neo-adjuvant arm had a chemotherapy response and 11% had a pathological complete response at surgery. However, the overall survivorship for the study was not significantly different with a median survival of 37 months for the neo-adjuvant arm and 26 months for the surgery arm alone. However, looking at subgroup analysis, there was a small, significant survival benefit for neo-adjuvant chemotherapy in those patients who presented with N0 and N1 disease. There was also an increased postoperative mortality of 6.7% for the neo-adjuvant arm compared to 4.5% for the surgical arm alone. The overall lethal toxicity for individuals entering the study was 7.8% compared to 6.6% in the study of ROSELL and co-workers [11, 12]. The fact that there was no additional survival advantage for patients with N2 disease does suggest that what advantage there may be for neo-adjuvant chemotherapy would occur in patients with very small volume disease. Although overall essentially a negative study, this study does raise the question of whether patients with stage I and stage II disease could benefit from neo-adjuvant chemotherapy. There is a current UK study open for patients with early disease who are randomised to chemotherapy or no chemotherapy prior to surgery, although patient refusal to enter the study because of the dislike of chemotherapy is slowing recruitment.

The question of whether neo-adjuvant treatment in locally advanced inoperable disease is going to be of value will be very hard to resolve. There are randomised controlled trials in progress in patients with bulky N2 disease where, following induction chemotherapy or chemo-radiotherapy, patients are randomised to surgery or completion radiotherapy or radical postoperative radiotherapy. These studies are recruiting slowly and it is very difficult to know whether this question will ever be answered, although intuitively it seems that this treatment will have very little to offer.

Adjuvant chemotherapy

The role of chemotherapy following surgery is likely to be answered over the next 2–3 yrs, as several large groups are performing studies addressing this question. In 1995, the Nonsmall Cell Lung Cancer Collaborative Group meta-analysis [14] reported 14 trials, including 4,357 patients, where randomisation was to receive or not to receive chemotherapy following surgery. The meta-analysis showed that there was an advantage for receiving cisplatin-containing chemotherapy following surgery. The hazard ratio for the eight studies containing cisplatin regimes was 0.87 (confidence intervals 0.74–1.02) and the absolute benefit for chemotherapy was 3% at 2 yrs and 5% at 5 yrs. This meta-analysis still did not produce a clear-cut statistically significant advantage for adjuvant chemotherapy ($p<0.8$) and several large studies are re-addressing this question. These studies hope to recruit >5,000 patients in total, which should provide a sufficiently large number of subjects to obtain an answer. Recently, the Adjuvant Lung Project Italy Group have issued a final report in abstract form on their study of patients with stage I, II and IIIA NSCLC who had either no chemotherapy or three courses of mitomycin, vindesine and cisplatin following surgery [15]. The study recruited 1,209 patients between January 1994 and February 1998; 602 had chemotherapy, 594 no further treatment, 42% of patients had stage I disease, 31% stage II and 27% stage IIIA. Sixty-nine per cent (327 patients) completed chemotherapy but 166 underwent modifications of treatment. One hundred patients stopped chemotherapy early and 47 did not start. There were no survival differences between the two groups and there were no prognostic effects based on the distribution of p53 or K-ras markers in the population. This study is therefore negative for the value of adjuvant chemotherapy, but other studies including those from the National Cancer Institute of Canada, the North American Lung and Leukaemia Group B and the UK Big Lung Trial will be reporting their data within the next 1–2 yrs.

In summary, neither neo-adjuvant or adjuvant chemotherapy should be given to NSCLC patients outside clinical trials.

Radical radiotherapy for stage I and II disease

There are patients who appear technically able to undergo resection, but either refuse surgery or are medically unfit. These patients historically are given radical radiotherapy with curative intent and this is common practice. However, there has only been one randomised controlled study conducted in the 1950s by the UK Medical Research Council which has assessed the value of radical radiotherapy as an alternative to resection [16]. Fifty-eight patients were randomised to resection or radical radiotherapy with survival at 4 yrs being 23% and 7%, respectively. This difference was not significant as the numbers were small and only became significant when squamous cell lung cancers alone were assessed. Since then, there have been a large number of nonrandomised studies using a wide range of irradiation doses, although all these studies have suffered from the disadvantage of having no pathological stage for the patients (as they did not undergo resection or invasive staging) and therefore only have clinical staging data. Assessing these studies, the better responses to the radiotherapy radiologically was for smaller tumours, particularly those <4 cm in diameter, where the complete response rate was ~50% and the local relapse rate following treatment was lower than for larger tumours [16–18]. Overall, 5-yr survival in these early stage patients varied from 6 to 32% [19]. It is possible that modern

treatment using CT planning and conformal radiotherapy, where the shape of the radiotherapy beam is moulded to the tumour, may produce better results than those quoted above, which are clearly inferior stage for stage to surgical data, but as yet there are no data to confirm or refute this.

Postoperative radiotherapy

Postoperative radiotherapy (PORT) has also been regarded as standard treatment following surgical resection where mediastinal N2 disease is found, as it can reduce local recurrence rates. However, what has remained controversial is whether improvement in local control will improve overall survival. A meta-analysis attempted to answer this question [20]. This analysis of all randomised controlled trials of surgery followed by radiotherapy or nothing included nine studies and in fact found a significant adverse effect for the addition of PORT on survival with a hazard ratio of 1.21 or a 20% increased relative risk for death. This finding has led to some considerable discussion. The results are not disputed for stage I and stage II disease but, for stage III disease, the negative impact of radiotherapy may have been due to poor field localisation, lack of CT scanning and different standards being applied in these older trials. The question, therefore, as to whether PORT has a role in stage IIIA disease following resection is doubtful and not completely resolved.

Positron emission tomography scanning in staging of nonsmall cell lung cancer

Because of the limitations of CT scanning and its high false-negative rate, particularly in the mediastinum, positron emission tomography (PET) scanning is of considerable interest. PET can detect malignancy in focal pulmonary lesions of >1 cm in size with a sensitivity of 96% and a specificity of 88% [21]. False-positive findings in the lung are seen in granulomatous disease, rheumatoid arthritis and false-negatives can occur in carcinoid tumours and alveolar cell carcinoma as well as for small lesions <1 cm in size.

PET is extremely valuable for evaluation of mediastinal lymphadenopathy. It is regarded as complementary to CT, as CT provides the anatomical information PET cannot provide. A review of published studies [22] in 2001 confirmed that PET was significantly more accurate than CT for the detection of mediastinal nodal metastases with a sensitivity and specificity of 79 and 91%, respectively, for PET *versus* 60 and 77% for CT. Studies assessing the additional value of PET in the staging of NSCLC are accumulating. The most recent study [23] randomised 188 patients to a conventional work-up *versus* conventional work-up and PET. They were able to exclude a greater number of patients from thoracotomy (18 of 92) compared to the group having a conventional work-up alone (32 of 96). Furthermore, the number of unnecessary thoracotomies was reduced to 19 for those who had a PET scan compared to 39 in the group who did not. PET, therefore, saved unnecessary surgery in 20% of patients. PET was much better at identifying N2 and N3 disease and confirmed distant metastases in seven patients compared to one in the conventional group. PET was superior to CT in identifying the site for mediastinoscopy biopsy and, in another 10 patients, only the PET scan suggested that a biopsy of a particular site would prove positive. This study and others concludes that the negative predictive value of a PET scan is so high that, if an individual had a normal CT during staging and no contra-indications to thoracotomy, a PET scan should be performed and, if the mediastinum was negative on PET and there were no other contra-indications found, the patient could proceed direct to surgery without a mediastinoscopy. However, the false-positive rate for PET scans (~5%) is high enough to suggest that positive findings on a PET scan, particularly in the mediastinum, should be confirmed by mediastinoscopy [24, 25].

Positron emission tomography scanning is also of value in identifying distant metastases but in series where distant positive positron emission tomography findings are discovered, positron emission tomography can be falsely positive and a positive finding on positron emission tomography, if it were to change management, should be proven by biopsy.

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