

Adjuvant chemotherapy and radiotherapy in the treatment of non-small cell lung cancer (NSCLC)

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ABSTRACT

Lung cancer is one of the most common human malignancies and remains the leading cause of cancer related deaths worldwide. Many recent technological advances led to improved diagnostics and staging of lung cancer. With development of new treatment options such as targeted therapies there might be improvement in progression free survival of patients with advanced stage non-small cell lung cancer (NSCLC). Improvement in overall survival is still reserved for selected patients and selected treatments. One of the mostly investigated therapeutic options is adjuvant treatment. There are many open issues in selection of patients and administration of appropriate adjuvant treatment.

KEY WORDS

Adjuvant therapy; chemotherapy; non-small cell lung cancer (NSCLC); radiotherapy

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Postoperative (adjuvant) chemotherapy

Lung cancer is the most common cancer in the world for several decades and also the most common cause of death from cancer (1). Only a small portion of cases are appropriate for surgical resection which still remains the best treatment option for potential cure in patients with non-small-cell lung cancer (NSCLC) (2,3). Results are disappointing when we look on 5-year survival rates, even after complete surgical resection. Indeed, 5-year survival rate for IA disease is 67% and 23% for IIIA disease (4). However, up to 60% of all resected patients

relapse and die of their disease. Relapse is most often dedicated to presence of micrometastases at distant sites, sometimes even before surgery, and sometimes after surgical resection when all macroscopically recognizable disease has been removed. All that fact and figures have been suggesting that lung cancer is usually a systemic disease at the time of diagnosis (4,5). In order to improve survival for patients with resectable NSCLC the use of chemotherapy and radiation therapy were examined in both the preoperative and postoperative settings (4,6,7).

Focus on adjuvant chemotherapy (postoperative)

A first meta-analysis of all randomized trials that compared adjuvant chemotherapy versus best sportive care was performed during 1995. This 1995 BMJ meta-analysis collected updated data on individual patients from 9,387 patients included in 52 randomized clinical trials and presented results of an absolute survival benefit of 4% at 5 years for cisplatin-based chemotherapy regimens with non-statistically significant trend in survival benefit. These results offer hope that modern chemotherapy

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regimens may have a role in treating all stages of non-small cell lung cancer (8). By the influence of 1995 BMJ meta-analysis a large number of clinical trials have been conducted with a great variety of results. Several of the studies failed to show any survival benefit of adjuvant therapy in comparison with best supportive care in radically resected patients with stage I-IIIa NSCLC (4-6). ALPI-EORTC randomized study in which patients with stage I, II, or IIIa NSCLC were planned to receive mitomycin C, vindesine and cisplatin or no treatment after complete resection did not confirm benefit of adjuvant MVP chemotherapy for patients with NSCLC but with poor compliance of MVP regimen used during this study (9). The other one, the European Big Lung Trial, which was similar to ALPI-EORTC study also failed (10). Eastern Cooperative Oncology Group (ECOG) trial also brought disappointing results. Study compared combination of chemotherapy plus thoracic radiotherapy with thoracic radiotherapy alone in order to fortify their influence on prolonging survival and preventing local recurrence in patients with completely resected stage II or IIIa nscl (11).

After this early disappointing results, light has appeared at the end of the tunnel thanks to largest adjuvant chemotherapy study ever done. In 2004 the International Adjuvant Lung Cancer Trial (IALT) presented the results in 1,867 fully resected patients with stage I to IIIa. Patients were randomly assigned to a control group or treatment group with a doublet cisplatin based adjuvant chemotherapy regimen. The drug combined with cisplatin was etoposid either vinca alkaloid. It was also allowed to use postoperative radiotherapy according to individual study team decision. This study showed that cisplatin based doublets yield in both overall survival and disease free period (12,13).

After this, two similar trials were designed to assess the combination of cisplatin and vinorelbine in adjuvant setting. The National Cancer Institute of Canada Clinical Trials Group JBR.10 enrolled 482 fully resected stage IB-II (T2N0, T1N1 or T2N1) for cisplatin and vinorelbine chemotherapy or observation. It has been shown that chemotherapy significantly prolonged recurrence-free survival as compared with observation (HR=0.60, $P<0.001$). Also, the median survival after chemotherapy regimen was significantly prolonged in compare with observation (HR 0.69, $P=0.009$; $P=0.04$ after adjustment for interim analyses). The overall survival advantage at five years was 15% ($P=0.03$). In the subgroup analyses this trial was failed to show statistically significant improvement in overall survival among patients with stage Ib NSCLC in comparison with observation group ($P=0.79$) (14). The same chemotherapy agencies, cisplatin and vinorelbine, were evaluated in Adjuvant Navelbine International Trialist Assotiation (ANITA) which enrolled 840 fully resected patients with stage Ib to IIIa. Five-year survival was improved by 8.6% in chemotherapy group, and the survival HR was 0.80 ($P=0.017$). This survival advantage did not diminish over time and was 8.4% at 7 years of follow-up.

In the subset analyses, there was no survival advantage for stage Ib disease (15). As it was said, both NCIC-CTG-JBR 10 and ANITA failed to show survival benefit of adjuvant chemotherapy for patients with completely resected stage Ib NSCLC. In 2004, Cancer and Leukemia Group B (CALGB) 9633 reported their preliminary results of study which was designed to evaluate adjuvant paclitaxel/carboplatin in Ib NSCLC. This was the only randomized clinical trial designed specifically for stage Ib NSCLC. Preliminary results suggested that adjuvant paclitaxel/carboplatin improved overall survival and disease-free survival. The hazard ratio for overall survival was the lowest reported in any randomized clinical trial (HR=0.62). Those results were gained from median follow up of only 34 months, and survival comparisons were based on only 57% of deaths required for final analysis. Unfortunately, after longer follow up, preliminary findings have not been maintained. In an unplanned subset analysis of CALGB 9633, patients with tumors size of 4 cm or larger had a statistically significant survival benefit with the addition of adjuvant chemotherapy (16). The only randomized clinical trial that did show benefit in stage Ib was Japan Lung Cancer Research Group (JLCRG) which evaluated adjuvant chemotherapy with oral uracil/tegafur (UFT) but there is no experience with adjuvant uracil/tegafur outside Japan and also this agent is not available in Europe for NSCLC (17).

The Lung Adjuvant Cisplatin Evaluation (LACE) looked at data from the five largest studies completed after the 1995 meta-analysis (BLT, ALPI, IALT, JBR.10, ANITA). This was the meta-analysis which had a purpose to identify treatment options associated with a higher benefit or groups of patients benefiting more from adjuvant treatment. The LACE meta-analysis included 4,584 patients. This meta-analysis showed statistically significant benefit (HR=0.89, $P=0.005$) on overall survival for chemotherapy compared with no chemotherapy and absolute benefits of 3.9% and 5.4% at 3 and 5 years, respectively. The effect on disease free survival also favored chemotherapy (HR=0.84, $P<0.001$) with absolute benefits of 5.8% and 5.8% at 3 and 5 years, respectively. Benefit varied considerably by stage of disease, with potential harm seen in patients with stage IA NSCLC, a trend towards benefit in patients with stage IB NSCLC, and clear benefit in patients with stage II and IIIa NSCLC. In the LACE meta-analysis, effect of combination of cisplatin and vinorelbine was marginally better than the effect of other drugs combination (18). The current opinion from ASCO, ESMO, NCCN and ACCP is that any cisplatin based combination may be administered to patients who are disease-free after surgery (4,6,7,19) Regarding performance status (PS), chemotherapy effect increased with better PS of 0 and 1, and may be detrimental for PS of 2. Generally, the LACE analysis confirms that adjuvant cisplatin based chemotherapy is of benefit in completely resected patients with NSCLC (18). So did the update of the 1995 NSCLC collaborative groups individual

patient data meta-analysis which showed statistically significant survival benefit for adjuvant cisplatin based chemotherapy, absolute benefit was 4% at 5 years (6,19). According to the leading guidelines adjuvant chemotherapy is recommended for patients with completely resected stage II and IIIA NSCLC. The management of stage IB is still controversial and we need more prospective trials for stage IB as only way to untangle this issue. Adjuvant chemotherapy is not recommended for patients with completely resected stage IA (4,6,7,19).

Better identification of patients who will benefit from adjuvant chemotherapy is a field of active investigation. It would be helpful to identify those patients who are predestined to benefit from adjuvant chemotherapy before its administration. Conversely, it would be helpful to identify those patients who will not benefit and to spare them from adjuvant chemotherapy. Several molecular prognostic and predictive factors were examined among available randomized trials (19). In IALT was found that low IHC expression of the excision repair cross complementation group 1 (ERCC1) indicates a marker of better outcome in patients who received adjuvant cisplatin, vice versa, high ERCC1 expression causes longer overall survival in control group (20). Expression of MutS homologue 2 (MSH2) had similarly effect like ERCC1. Low expression was related to benefit of platinum based adjuvant chemotherapy while high expression was related to longer overall survival in untreated patients. Regarding combination of ERCC1 and MCH2 benefit from adjuvant chemotherapy decreased with the increasing number of positive markers (19). In JBR-10, K-RAS wild type and p-53 wild type patients had benefit from adjuvant chemotherapy in comparison with mutants but statistically insignificant (21). The role of class III beta-tubulin (TUBB3) was evaluated as a predictive marker for benefit from adjuvant chemotherapy in resected NSCLC in four randomized trials (IALT, JBR-10, ANITA and CALGB 9633). It was shown that high TUBB3 expression was a negative prognostic factor and it was correlating with inferior survival (22). These were just some of the molecular factors, additional biomarkers involving different pathways have been retrospectively evaluated in other studies but large prospective randomized clinical trials are necessary for validation of their effects (19). So far, target therapy which has considerably changed the treatment of advanced stage NSCLC showed disappointing results in resected patients (19).

Postoperative (adjuvant) radiotherapy

The principles of adjuvant radiotherapy in locally advanced NSCLC have changed significantly over the past several decades. The indications become clearer, with increasing data regarding survival outcomes and improved identification of patients who receive the greatest benefit from this treatment. New advanced

technology now allows physicians to better target the specific region of interest while avoiding surrounding critical structures. The issue of the appropriate field and possibility to reduce the size of the field without jeopardizing locoregional control remains controversial (23).

Besides the fact that radiation therapy (RT) can improve local control and potentially aid survival in patients who have had resection for lung cancer, it can also cause serious toxicity. The post-operative radiation therapy (PORT) meta-analysis illustrated the potential toxic effects of PORT. Modern 3D radiation treatment planning facilitates the design of treatment fields that more conformally treat the site(s) at risk. Modern systemic and local therapies are likely synergistic. Optimizing systemic staging and treatment may increase the ability of local therapies to improve survival (23,24).

Surgical margins

Large number of trials have evaluated the indications for adjuvant radiotherapy in patients with NSCLC. One of the common issues was agreement that the use of PORT in the setting of positive surgical margins reduces the risk of locoregional recurrence (23).

The margin at which locoregional recurrence increases is still to be defined. There is no agreement nor consensus which can be helpful in this issue. One of the largest well designed studies came from University of Pittsburgh (UPMC) group. El-Sherif's study concluded that with sublobar resection, margins less than 1 cm were associated with a 15% risk of local recurrence, while recurrence rates were 7% when the distance was equal to or greater than this threshold (25). Sawabata's group utilized a margin to tumor size ratio (M/T) of greater than 1 to predict cancer recurrence (26).

Mayo Clinic group designed study with the aim to determine whether an increased bronchial resection margin length is correlated with an improved disease-free and overall survival rate. Authors evaluated 496 patients with completely resected lesions (R0-resection), and a documented bronchial margin length. The major conclusion of this trial is that the extent of the bronchial margin has no clinically relevant impact on disease-free and overall survival in NSCLC, when R0 resection is achieved (27).

Stage and nodal status

Patients with N2 disease and patients not receiving chemotherapy for N1 disease have most benefit from adjuvant or postoperative radiation therapy. However, it was concluded by substantial number of clinical trials that PORT decreases the risk of local recurrence without significant effect on survival (23).

One of the most important studies—(SEER) study that examined over 7,000 patients, confirmed that the use of PORT on all patients did not significantly affect overall survival.

However the authors confirmed significant increase in overall survival in patients with N2 nodal disease. For patients with N0 and N1 nodal disease, PORT was associated with a significant decrease in survival (28).

The SEER database analyses of patients with resected T1-3, N1/2 NSCLC suggests PORT could be beneficial in selected patients (5). In the N2 population, PORT was associated with improved 5-year overall survival (22% versus 16%). Patients with ≥ 4 positive nodes, whether N1 or N2, also seemed to benefit from PORT (29,30).

The current consensus recommendation, as given in the National Comprehensive Cancer Network (NCCN) guidelines, is to deliver PORT for N2 disease, because the consensus of the current published data indicates a benefit for this subgroup of patients. In the setting of N1 or N0 disease, PORT is considered in the setting of close or positive surgical margins (31).

Adjuvant RT in stage I resected NSCLC patients

The Belgian group conducted one of the most important trials on PORT in stage I NSCLC patients. Van Houtte's team conducted a randomized trial in 175 patients who had a complete resection and no lymph node involvement. The major conclusion of this trial was that thoracic radiation therapy (TRT) should not be recommended in N0 patients. A more recent Italian randomized trial compared PORT at a dose of 50.4 Gy with no PORT in 104 patients with pathological stage I disease. RT resulted in a significantly lower risk for local recurrence but there was no significant difference in terms of the 5-year overall survival rate (67% in the PORT group and 58% in the control group). Considering a low risk for local recurrence in stage I NSCLC patients, routine PORT is not recommended for such patients after complete resection (32,33).

Adjuvant RT in stage II and III resected NSCLC patients

One of the largest randomized trials designed to evaluate PORT in setting of stage II and III NSCLC was conducted by the Lung Cancer Study Group. The study included 230 patients with stage II and stage III squamous cell carcinoma and evaluated PORT at a dose of 50 Gy (32).

PORT resulted in a significantly lower risk for local recurrence, 1%, versus 41% in the control arm, but this effect did not translate into overall survival benefit (5-year survival rate, 40% in both arms). It was clear that most recurrences were outside the radiation field or were distant failures. However, a subgroup analysis suggested that PORT could prolong the disease-free interval in patients with N2 disease. Medical Research Council (MRC) study included patients with adenocarcinoma (34).

The results of MRC study were consistent with the results of previous trials: no survival benefit for patients in the PORT group over those in the control arm, but in the N2 subgroup

analysis there was a nonsignificant trend toward longer survival and better local control. One of the largest trials evaluating influence of PORT on overall survival in resected lung cancer patients came from French group (Groupe d'Etude et de Traitement des Cancers Bronchiques) and included 728 resected patients in stages I, II and III (35).

It demonstrated that PORT had a detrimental effect on survival: the 5-year survival rate was 43% for the control group and 30% for the RT group. In terms of the 5-year rate without local recurrence, there was a trend in favor of PORT among N2 patients. In a Chinese randomized study of 366 completely resected patients with N1 or N2 nodal disease, PORT resulted in a significantly lower rate of local relapse—the local failure rate was 12.7%, versus 33.2% in the control group, but had no impact on survival (36).

Adjuvant chemoradiotherapy in stage II and III patients

For a long period of time adjuvant radiotherapy was considered the standard of treatment for selected patients in stage II and stage III NSCLC. The ECOG completed a prospective trial comparing PORT with PORT plus chemotherapy (etoposide and cisplatin). The 3-year survival rates were 52% in the PORT arm and 50% in the combined treatment arm. The locoregional recurrence rate within the radiotherapy field was around 13% in both arms. Standardized surgical treatment may explain these results in terms of local control (32,37).

The authors concluded that cisplatin and etoposide given concomitantly with adjuvant radiotherapy did not prolong survival or modify local failures, compared with PORT alone. Since this publication, there have been several phase II trials evaluating adjuvant concomitant chemoradiation (38,39).

In the Radiation Therapy Oncology Group 9705 phase II trial, 86 patients with completely resected NSCLC (stage II and stage IIIA) had concurrent paclitaxel plus carboplatin and PORT at a dose of 50.4 Gy (36). The 3-year progression-free and overall survival rates were, respectively, 50% and 61%, and local failure was a component of first failure in 15% of patients. The authors of 97-05 trial concluded that concurrent combination of chemotherapy (paclitaxel/carboplatin) and thoracic radiation therapy as adjuvant therapy for completely resected stage II and IIIA NSCLC does not appear justified since the survival results were not significantly better to those achieved with postoperative thoracic radiation therapy alone. In another phase II study that included 42 patients (of whom 60% were N2) treated with a similar regimen, the 2- and 5-year Kaplan-Meier estimates of locoregional control and overall survival were 92% and 88% and 72% and 44%, respectively (39). Even though the results of Feigenberg's study confirmed the 97-05 results, authors concluded that with new and better tolerated chemotherapy regimens the strategy of concurrent TRT and chemotherapy after completely resected stage II and IIIA non-small cell lung

cancer should be further explored.

Radiation dose

Data which could establish a dose–response relationship in PORT for NSCLC are still not available. Based on historical clinical experience in radiation therapy for solid tumors, 45 Gy is considered a minimum dose required to sterilize occult microscopic metastases, and in the postoperative setting, higher doses are believed to be required to compensate for decreased tissue perfusion and increased hypoxia. A dose of 50-54 Gy in 1.8-2 Gy fractions appears to be appropriate, adequate and consistent with the treatments used in latest trials and current practise (35,40,41).

Radiation therapy technology

The current standard of care for thoracic radiation therapy is three-dimensional conformal radiation therapy (3D CRT), which consists of computer-assisted treatment planning and dose calculation on a model of the body based on CT imaging acquired in the treatment position. 3D CRT allows visualization of the dose distribution in three dimensions as well as manipulation of the dose distribution by adjusting parameters including the number of fields, the shape of the fields, and the beam angles and weighting. Newer developments in radiation therapy include technologies to improve control over the dose distribution such that the high doses conform more closely to the targeted regions and spare adjacent normal organs; to assess the motion of the targets and normal organs, particularly motion induced by breathing; to compensate for organ motion during treatment; and to verify at the time of treatment that the planned treatment is delivered accurately (41).

Data are emerging that Intensity-modulated radiation therapy (IMRT) results in decreased toxicity without compromising tumor control, including a retrospective analysis finding substantially reduced rates of radiation pneumonitis in patients treated with IMRT compared to 3D CRT (42).

Particularly when employing complex treatment technologies such as respiratory-gated IMRT, it is crucial to verify that the planned treatment is actually being delivered accurately. Image-guided radiation therapy (IGRT) refers to the use of imaging devices incorporated into the radiation treatment system to verify that the original position and motion of the patient's internal anatomy is reproduced at the time of treatment, and to allow correction of any mismatches identified. IGRT is essential to highly conformal respiratory motion-compensated radiation therapy (43).

These new technologies will play an increasingly important role in thoracic radiation therapy, and should be used judiciously with attention to proper quality assurance.

Toxicity issues in PORT

The excess toxicity (mostly cardiac and pulmonary) and noncancer-related deaths observed after PORT in the meta-analysis trials can probably be explained by excessive volumes of radiation, old radiation techniques, too large doses and fraction sizes, and no CT scan-based planning. Unfortunately, the authors could not collect data on toxicity or causes of intercurrent deaths in the different studies. Late cardiac complications described after mediastinal RT are linked to the total dose, the fraction size, the irradiated volume, the technique of irradiation, as well as comorbidities (tobacco use, overweight) (44,45). Several authors have underlined the importance of the RT technique to lower this risk (46).

Pulmonary complications, such as pneumonitis and lung fibrosis, can also be observed, but they occur earlier and there are strong volume and fractionation effects. The administration of certain radiosensitizing drugs may increase this risk (47).

Conclusions

At present, patients who have had a complete resection of their primary tumor with mediastinal lymph node dissection showing no mediastinal involvement (pN0 and pN1) should not have PORT. The issue of PORT is not as clear among pN2 patients and warrants further studies with more modern techniques. The indication for PORT is currently debated for each individual patient with mediastinal involvement.

Some clinicians never consider PORT for pN2 patients, others consider it standard in pN2 patients, and others restrict their indication for PORT to patients with multiple N2 nodal involvement or cases of extracapsular extension.

Conformal RT should be mandatory. The irradiation volume should take into account data from a thoracic CT scan and the eventual PET scan data before surgery, as well as the description of the mediastinal exploration and histopathological results.

Consequently, paratracheal nodes, suprarenal nodes, as well as the homolateral hilar region should be systematically included in the irradiation volume.

Based on previous studies, it seems reasonable to treat only involved lymph node stations and uninvolved stations at high risk to better protect surrounding normal structures and consequently minimize treatment-related mortality.

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