symposium article

Non-small cell lung cancer: early stages

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introduction

More than 170 000 new cases and 150 000 deaths have occurred in 2003 in US owing to lung cancer, which is the leading cancer death reason for men in US. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers [1, 2].

Despite the progress in imaging and diagnostic procedures, non-small cell lung cancer (NSCLC) usually presents as advanced (locally or more frequently disseminated), and a small part (around 30%) has to be considered early stage [1]. For early stage disease, surgery still remains the treatment choice, even if the majority of patients will undergo progression after complete tumor resection. In order to increase curable rate us such social disease, progresses in diagnosis technique and treatment approaches have been recently developed.

diagnosis and screening

Non small cell lung cancer cure rate is significantly increased when the patient undergoes surgery; this scenario strongly stresses the crucial role of early diagnosis and screening too [3]. Recent advances in imaging techniques, such as spiral computed tomography (CT) improved the early diagnosis rate while new issues have been opened owing to charming and promising results coming from screening trials [4] In this direction, the treatment strategy to apply in patients with lung cancer discovered into a screening plan, needs to be explored in a randomized fashion.

In 2000, the National Cancer Institute in Milan launched a pilot trial to investigate the efficacy of yearly spiral CT and positron emission tomography (PET), combined with blood and sputum biomarkers, in a large cohort of high-risk volunteers [5]. This study enrolled 1035 heavy smokers (20 pack/years) aged 50+ to undergo annual low-dose CT±PET for 5 years. Lesions up to 5 mm were deemed non-suspicious and sent to repeat low-dose CT after 12 months, while PET was applied to lesions greater than 7 mm, after HRCT. At the end of 5th year, the final compliance rate was 85%, the cumulative recall rate for HRCT 17% and PET rate only 1.4% (69/4818 low-dose CTs). A total of 38 primary lung cancers were diagnosed, with complete resection in 33 (87%) and 24 (63%)

pathological stage I. There were no pneumonectomies or perioperative deaths, and 63% of patients were alive and disease-free (96% of stage I).

The innovative design of this pilot study, combining spiral CT and selective PET with a conservative approach to smaller lesions, proved to be safe and effective. Based on these results, a new multicentric prospective randomized trial was launched in Northern Italy. The new study, named Multicentric Italian Lung Detection trial (MILD), is expected to recruit 10 000 individuals (50+ heavy smokers), with a total intervention period of 10 years, randomized in 2 groups: a control group undergoes to a program of primary prevention with pulmonary function test evaluation and a group to periodic spiral CT associated with primary prevention and pulmonary function test evaluation. The last one is randomized in two arms: yearly low-dose CT vs. CT every 2 years.

Primary end-point of the study is the assessment of smoking cessation percentage and ultimate impact of early lung cancer detection on mortality. Last generation CT (16sl) and CT/PET is combined with genomic and proteomic analysis on plasma samples.

adjuvant chemotherapy

In order to improve survival of patients affected by early stage NSCLC, randomized phase III trials have been conducted to look if complementary radiotherapy and/or chemotherapy add any benefit over exclusive surgery. A meta-analysis of more than 2000 patients showed that radiotherapy doesn't add any benefit over surgery alone in overall survival, while a recurrence reduction is provided, and should not be considered as standard treatment [6]. Extra-thoracic relapse can explain this effect and suggests the adjunction of adjuvant chemotherapy.

To date, although for advanced disease the benefit of chemotherapy over best supportive care is worldwide well-defined [7, 8], and for locally advanced is promising when combined with radiotherapy, its role in adjuvant setting is still controversial.

Furthermore, the historical meta-analysis conducted by the NSCLC Collaborative Group showed that chemotherapy yielded a not significant benefit in survival over surgery alone [7], although a positive trend was seen.

Nine randomized clinical trials (RCTs) have been recently completed and published with conflicting results. Two

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published recent large trial have shown a small advantage in overall and progression-free survival versus exclusive surgery [9, 10]. Two further phase III trials have been presented, all of them providing significant benefit of platinum-based chemotherapy over surgery alone [11, 12] (Table 1).

Many of these RCTs were designed to confirm the trend in favor of chemotherapy after surgery that has been demonstrated by the LCCG meta-analysis [7]. ECOG trial, which started before the evidence that radiotherapy would not add benefit to surgery alone, was designed to look whether chemotherapy adjunction was beneficial over standard surgery combined with radiotherapy [13]. After 25 years of conflicting results about adjuvant chemotherapy in early NSCLC, the large IALT trial started to show a significant improvement in both OS and PFS [9]. This trend in favour of chemotherapy has been subsequently confirmed in the following 3 RCTs [10–12].

Looking at the adjuvant scenario, an absolute increase of 4–8% in 5-year survival provided by chemotherapy in early breast or colon cancer was considered enough to apply such approach widely as common clinical practice. Therefore, in a disease such as early NSCLC, an absolute benefit of 2–4% in 5 year survival should be the best realistic goal to aim, as actually already suggested ten years ago by the LCCG meta-analysis [7].

In accordance to the levels suggested by the National Cancer Institute for treatment guidelines, accurate meta-analyses provide the strongest evidences together with large randomized RCTs. Although individual patient data (IPD) meta-analyses are considered the best way to pool results from RCTs, at least four literature-based meta-analyses had recently produced positive results in favor of adjuvant chemotherapy [16–19]. Moreover, an homogenous effect has been calculated, and a significant absolute benefit ranging from 2 to 4.5% whatever screened population, has been found [19].

Four trials [9–12] did dramatically contribute to meta-analyses results, and there are several reasons explaining why such outcomes were reached in contrast to the other previous trials. Different patient characteristics are present across all RCTs, in particular in staging, pneumonectomy and radiotherapy rate (Table 2).

The results obtained by meta-analyses raise the question about which stage of cancer would be especially benefited by adjuvant chemotherapy and which drug is best added to CDDP.

Unfortunately, meta-analyses based on abstracted data maintain these questions unanswered unless specific hazard ratios of subset of patients are displayed.

The question regarding which is the correct regimen to administer is an open issue; while cisplatin-vinorelbine provides benefit in stage II, and IIIA [10, 12], the benefit for stage IB is still under debate [20], although the carboplatin-paclitaxel combination produced benefit in the CALGB 9633 RCT [11]. Are results provided by such RCTs reproducible in clinical practice? Unfortunately, one of the largest trial, which yielded the benefit of the cisplatin-vinorelbine in stage II and IIIA patients, has a relevant slow recruitment bias [12] Moreover, statistical issues and compliance to chemotherapy need to be carefully evaluated when approaching these RCTs (Table 3).

If positive survival results will be confirmed by the forthcoming IPD meta-analysis, we should conclude that chemotherapy provides an impact on the natural history of NSCLC. We are actually unable to understand how much the higher benefit coming from stage I-II patients subgroup did contribute to the general result. Specific RCTs and sensitivity analyses do generate the hypothesis that chemotherapy works better in specific patient' subgroups (i.e. stage I–II, PS 0–1) [10–12, 19].

It is certain that the paradigm in the treatment of early stage NSCLC shifted in the last 3 years; the positive results of RCTs accruing more than 7000 patients and the accomplished meta-analysis did offered promising results in favor of adjuvant chemotherapy. Advances are emerging about the selection of those patients who are likely to better benefit from such treatment.

neo-adjuvant chemotherapy

Although resectable non-small cell lung cancer is potentially curable with surgery but a substantial number of patients will relapse. During recent years, an attempt to improve surgical outcome is represented by the administration of chemotherapy before or after surgery [21–26].

In order to improve control of localized disease and eradicate micro-metastases, multimodality treatment has been developed: radiotherapy and surgery aiming at the local disease, and chemotherapy targeting the distant micro-metastases.

The interest on the role of chemotherapy in early stage NSCLC is confirmed by the recent publication or presentation of many trials and meta-analyses [7, 19, 21, 22].

The administration of induction chemotherapy prior to definitive local therapy offers several advantages for early stages NSCLC: an early treatment of micro-metastatic disease, downstaging of tumor with possible increasing of radical surgery, direct evaluation of responsiveness to chemotherapy, better compliance to chemotherapy [27–31]. In fact approximately 90% of patients treated with neoadjuvant chemotherapy received all or nearly all of their planned therapy [25, 30, 31].

Since 1990 six randomized trial with neoadjuvant chemotherapy were published and in each one cisplatin-based chemotherapy were administered [21–26, 32] (Table 2).

Depierre et al. [22] published the largest phase III neoadjuvant chemotherapy study [6 met] n which 373 patients with stage

Table 1. Adjuvant RCTs characteristics

Author [ref.]	#Pts	Stage (%)			Pneumo. (%)	RT (%)
		I	II	III		
Keller et al. [13]	488	–	41	59	32	100
Scagliotti et al. [14]	1209	39	33	28	25	43
Arriagada et al. [9]	1867	37	24	39	35	30
Waller et al. [15]	381	27	38	34	–	14
Winton et al. [10]	482	45	55	–	23	–
Strauss et al.* [11]	344	–	100	–	10	–
Douillard et al.* [12]	840	35	30	35	37	25

*Only in abstract form.
Ref.: reference number; #: number; Pts.: Pneumo.: pneumonectomy; RT: radiotherapy.

Table 2. Adjuvant RCTs

Author [ref.]	Planned # of courses	Compliance	Required sample size	Planned OS % gain	Obtained OS % gain
Keller et al. [13]	3–4	69%	NR	NR	0% (5 yrs)
Scagliotti et al. [14]	3	69%	1300	7% (5 yrs)	3% (5 yrs)
Arriagada et al.* [9]	3–4	74%	3300	5% (5 yrs)	4% (5 yrs)
Waller et al. [15]	3	64%	4000	5% (5yrs)	0 (1yr)
Winton et al. [10]	3–4	65%	450	10% (3 yr)	15% (3 yrs)
Strauss et al.§ [11]	4	85%	384	NR	12% (4 yrs)
Douillard et al.§ [12]	4	76%	800	10% (2 yr)	5.1% (2 yrs)

*Change in trial design; §Only in abstract form.
Ref.: reference number; #: number; Pts.: patients; OS: overall survival.

Table 3. Neoadjuvant RCTs

Authors [ref.]	Stage	#Pts	% Planned dose	Neo-Adjuvant arm	Survival *P* value
Nagai et al. [21]	IIIA	62*	71	Ddp-Vds	0.53
De Pierre et al. [22]	IB–III	373	89.9	Ddp-Ifo-MmC	0.15
Rosell et al. [23]	IIIA	60	100	Ddp-Ifo-MmC+RT	<0.001
Roth et al. [24]	IIIA	60*	NA	Ddp-VP-16-Cyc	0.056
Pass et al. [25]	IIIA	27**	100	Ddp-VP-16+RT if R+	0.095
Dautzenberg et al. [26]	I–III	26*	84.6	Ddp-Cyc-Vds	0.85
Pisters et al.§ [32]	IB–IIIA	354*	77	Carbo-Pct	0.32

*Early stopped; **Interim analysis; §Only in abstract form.
Ref.: reference number; #: number; Pts.: patients.

I–IIIA (except T1N0) operable disease were randomly assigned to receive 2 cycles of mitomycin, ifosfamide and cisplatin ($n = 187$), or surgery alone ($n = 186$). Responding patients received two additional postoperative cycles. In both arms, patients with pT3 or pN2 disease received thoracic radiotherapy.

A decrease in distant metastases ($P = 0.009$), an improvement in median survival (37 months versus 26 months, $P = 0.15$), and a significantly prolonged disease-free survival ($P = 0.033$) favored the neoadjuvant arm. Although clinically important differences were observed in median 3- and 4-year survival rates, they were not statistically significant, except for stage-I and stage-II disease. A quantitative interaction between N status and treatment was demonstrated, with benefit being limited to N0-N1 disease (relative risk 0.68; $P = 0.027$). Toxicity of preoperative chemotherapy resulted in a non-significant excess of deaths during treatment.

To assess the possible benefit of preoperative chemotherapy and surgery for the treatment of patients with non-small-cell lung cancer, Rosell et al. [23] randomized patients with stage IIIA to receive either surgery alone or three courses of chemotherapy (mitomycin, ifosfamide and cisplatin) given intravenously at three-week intervals and followed by surgery. All patients received mediastinal radiation after surgery.

For the 30 patients who received preoperative chemotherapy, overall median survival was 22 months (95% CI 13.4–30.6) compared to 10 months of the 30 patients who received surgery alone (95% CI 7.4–12.6; $P = 0.005$ by the log rank test). Authors concluded hypothesizing that preoperative chemotherapy could improve the prognosis of still resectable CT-visible N2 non-small cell lung cancer.

The other randomized trials present in Literature, are limited by the relative low number of patients or by the preventive interruption of the trial due to different reasons.

Roth et al. [24] early stopped the trial based on the magnitude of the treatment effect, after 60 on 130 planned patients were analyzed for the interim analysis. In fact stage IIIA NSCLC patients assigned to receive peri-operative chemotherapy (cyclophosphamide, etoposide, and cisplatin) and surgery (28 patients) had an estimated median survival of 64 months compared to 11 months for patients who had surgery alone ($P < 0.008$ by log-rank test), and the estimated 2- and 3-year survival rates were 60% and 56% for the perioperative chemotherapy patients and 25% and 15% for those who had surgery alone, respectively.

Dautzenberg et al. [26] stopped prematurely their trial due to the rate of preoperative progression in the group that received preoperative chemotherapy (cisplatin, cyclophosphamide, vindesine). Nagai et al. [21] designed a randomized trial to compare induction chemotherapy (cisplatin and vindesine) followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer, but unfortunately, trial early terminated ($n = 62$) because the accrual rate was too slow, and authors concluded that the study did not demonstrate a survival difference between the groups, although this may have been because the statistical power was limited.

At 2005 ASCO meeting, Pisters et al. [32] presented the preliminary results of a phase III trial of surgery alone or surgery plus preoperative paclitaxel/carboplatin chemotherapy (3 cycles) in early stage non-small cell lung cancer. Patients were stratified on the basis of disease stage (IB and IIA versus IIB

and IIIA), and the primary endpoint was 33% increase over expected 2.7 yrs median for surgery. Planned sample size of this prospective, randomized trial was 600 pts, but the trial stopped early in July 2004 after 354 pts (174-surgery alone, 180-preop PC) were accrued, due to the positive adjuvant data. Major response to induction chemotherapy has been reached in 41% of the patients (PR: 38%, CR: 3%), and 77% received the planned dose. Median progression-free-survival was 20 and 31 months in control arm and in preoperative arm respectively (HR 0.80, 95% CI 0.59–1.07, $P = 0.14$) while overall survival was 40 versus 47 months. (HR 0.84, 95% CI 0.60–1.18, $P = 0.32$). Median survival is similar to Phase II ''BLOT'' study [31] that used the same schedule, but control arm was better than planned (40 versus 32 months), and significantly better than the De Pierre study (40 versus 26 months) Although closed early, this is one of the largest preoperative randomized trial in early stage NSCLC, and we think that survival trend leads to further support the role of preoperative chemotherapy in NSCLC.

Results of CHEST trial [33], in which about 267 patients with stage IB-IIIA NSCLC are randomly assigned to 3 cycles of Cisplatin and Gemcitabine as induction therapy, or to surgery alone are eagerly awaited.

Although studies are ongoing, no data are actually available to compare the utility of adjuvant chemotherapy with neoadjuvant one. We think that the NATCH trial, actually ongoing, will address the important question, and quantify the benefit of induction or postoperative chemotherapy in early NSCLC.

radiotherapy

Stage I and II lung cancer indicates disease limited to the hemithorax, with tumor extension no farther than the adjacent resectable structures peripherally (T3) or hilar nodes proximally (N1). In these cases, surgical excision is the treatment of choice. However, some patients with surgically resectable disease have medical contraindications or refuse surgery. For such patients, radiation therapy offers an alternative and potentially curative approach.

In 1960, the first published experience was from the Hilton of University College Hospital of London; 40 to 55 Gy were delivered by orthovoltage equipment to 38 patients [34]. Several retrospective series have reported survival rates ranging from 0 to over 30%. Modern series have examined the issues of dose and dose escalation in relation to tumor size, local control, and survival for stage I and II disease. The highest reported survival was in a series that used the highest median dose, 70.2 Gy [35]. The evidence suggests that radical radiotherapy is an effective treatment primarily for tumors less than 3 cm in size (i.e. T1) when treated to doses of 65 Gy or higher [36]. Complete response and local control of larger tumors appear less likely with standard radiation fraction schedules and doses, despite modern equipment and CT-based planning. Looking at the data reported in a review [36], no correlation was found between cumulative radiation dose and median overall survival (OS) while a correlation was found between cumulative dose and local control rate ($r = 0.56$).

Surgery has the highest reported survival rates in stage I and II disease and no modern randomized study has compared surgery with radiation in a comparable group of patients. The differences in results between surgery and radiation are due in part to patient characteristics, because patients referred for radiation have worse performance status, are less rigorously staged and have poor pulmonary function combined with comorbidity illnesses [37, 38]. Moreover, it is important to evaluate cause specific survival (CSS) as an endpoint in such studies, because of the different undercurrent mortality rate. Based on 13 radiation series [36], the average ratio CSS at 5 years/OS at 5 years was 2.4 (SD 1.3). In the surgical stage I series reported by Read, the ratio was 1.5 [37].

The regional failure rate was typically less than 10% in reported series in which elective nodal areas were not treated. In one series, most patients did receive elective nodal irradiation, but still had a failure rate approaching 10%, which suggests that a typical elective dose of 40 Gy is not sufficient to control occult disease [39]. Hence, elective nodal irradiation of the mediastinum is probably unnecessary for early stage tumors. The median local failure rate reported in 15 series after radiation therapy alone was 45% ranging from 19% to 75, while nodal relapses are a rare event [39].

At present, an issue to be addressed in the treatment of early stage NSCLC is what dose and fractionation should be used. The need for a conventional fractionation of 1.8–2 Gy is being challenged. The role of hypofractionation – such as a dose of 3–4 Gy per fraction or as high as 10 Gy via stereotactic radiosurgery – is currently being investigated. The dose of 4 Gy per fraction was investigated in a poor performance status population and it was found to achieve an adequate control. The split-course versus continuous-course radiation has been examined with mixed results and they have generally been discouraging when treating patients with a curative intent. Recent randomized clinical trials have reported a survival benefit in favor of accelerated hyperfractionated (CHART) regimen compared with conventional fractionation [40].

Many controlled phase I–III clinical trials using radiation therapy (RT) for the treatment of early stage NSCLC are currently ongoing. Phase I trials: dose escalation with 3-dimensional conformal RT (CRT); phase II: PET in CRT guided by breath held with CT and PET imaging, self-gated breath-hold technique for tomotherapy, and stereotactic body radiotherapy; phase III: photon vs. neutron vs. photon/neutron, sub-lobar resection with vs. without intra-operative brachytherapy, and CHART vs. CHART combined with chemotherapy [41].

Although patients not suitable for surgery must be considered to be an unfavorable population, radiation therapy alone appears to be an effective treatment method for selected patients. Evidence based indications and working tool validations are expected from ongoing clinical trials in order to increase local control and survival rates.

acknowledgements

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