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ORIGINAL ARTICLE

Evolution of induction chemotherapy for non-small cell lung cancer over the last 30 years: A surgical appraisal

Elizabeth Fabre[1], Caroline Rivera[2], Pierre Mordant[2], Laure Gibault[3], Antoine Dujon[4], Christophe Foucault[2], Françoise Le Pimpec-Barthes[2] & Marc Riquet[2]

1 Department of Medical Oncology, Georges Pompidou European Hospital, University Descartes, Paris, France
2 Department of General Thoracic Surgery, Georges Pompidou European Hospital, University Descartes, Paris, France
3 Department of Pathology, Georges Pompidou European Hospital, University Descartes, Paris, France
4 Department of Thoracic Surgery, Cedar Surgical Centre, Bois Guillaume, France

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Correspondence
Elizabeth Fabre, Department of Medical Oncology, Georges Pompidou European Hospital, 20 rue Leblanc, 75015 Paris, France.
Tel: +33156093474
Fax: +33156092573
Email: elizabeth.fabre@egp.aphp.fr

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Abstract

Background: Induction chemotherapy (ICT) is supposed to reduce the risk of micrometastatic progression and improve resectability of non-small cell lung cancer (NSCLC). However, best indications for ICT strategy remain unclear in published meta-analyses. Based on this observation, an evaluation of daily practice is of importance. Therefore, we reviewed indications and efficacy time trends in our 30-year series.

Methods: A database including all patients with NSCLC who underwent surgical resection in two French centers from 1980 to 2009 (n = 5563) was prospectively set and retrospectively reviewed. The indications, clinical and pathologic response rates, and overall survival of ICT patients (n = 732) were analyzed during three successive time-periods: P1 from 1980 to 1989, P2 from 1990 to 1999, and P3 from 2000 to 2009.

Results: The proportion of patients who benefited from ICT increased over time, from 2.8% (n = 35) in P1 to 12.5% (n = 274) in P2, and 20.2% (n = 423) in P3. Indications evolved over time with more N2 patients (n = 211; 49.8%) and less initially unresectable patients (n = 72; 17%) in P3. The clinical response rate between P1 and P2 increased. Five and 10-year survival rates of ICT patients were 35.2% and 21.5%, respectively. In multivariate analysis, time-period, age, type of resection, histology, and pathologic response to chemotherapy were significant prognostic factors.

Conclusions: Our report on the off-trial use of induction therapy during the last 30 years demonstrates an increased use of ICT, a progressive focus on N2 disease, and improved response rates.

Introduction

Despite complete surgical resection, patients with non-small cell lung cancer (NSCLC) present a high risk of occult lymph node (LN) metastases and distant recurrence, even in early stages.[1,2] As a consequence, postoperative five-year survival is limited to 60% in patients with stage I, 40% in patients with stage II, and 30% in patients with stage IIIA disease, justifying the development of multi-modal treatment.[3]

Adjuvant chemotherapy is now accepted on the basis of randomized clinical trials that demonstrated improved survival in patients with pathological stage IB if the tumor size is ≥4 cm, stage II, and stage IIIA disease.[4] Furthermore, meta-analysis based on published trials confirmed the efficacy of adjuvant chemotherapy following complete surgical resection of stage IB and stage II disease.[5]

The theoretical advantages of induction chemotherapy (ICT) include the early eradication of micrometastases, low risk of disease progression compromising resection, and improved patient adherence to the schedule of chemotherapy.[6] These considerations may be true but are changing as a result of more rapid recovery following the introduction of video-assisted thoracoscopic surgery (VATS) lung resection. VATS has been shown to facilitate early and higher adjuvant chemo compliance compared with thoracotomy.

Induction chemotherapy was initiated during the 1980's and then developed rapidly after the results of the first

randomized trials. Since then, several meta-analyses have reported a significant survival advantage of ICT compared with surgery alone.[7–10] Therefore, ICT has been integrated into the therapeutic armamentarium against lung cancer and is now systematically discussed during tumor board conferences.

However, most of the trials included in these meta-analyses were small-scale and lacked statistical power. Some additional trials were prematurely ceased because of slow accrual; thus, the effectiveness of ICT is still debated in stage IIIA-N2 patients.[5,7,9–15] Major questions remain as to the benefit of preoperative chemotherapy regarding survival and tolerance and according to stage, its indications in comparison with adjuvant chemotherapy in stages IB and II, and the recommended chemotherapy regimen.

Finally, published meta-analyses provide limited information on the optimal modalities of ICT. Prospective randomised trials are no longer performed, or only in view of testing different induction treatment modalities. In our study, all indications were decided accordingly during tumor board conferences for those encouraging meta-analytic conclusions. Based on this observation, an evaluation of daily practice appears to be of importance. Therefore, using a 30-year series, we aimed to analyze trends in ICT practice over time and reviewed off-trial indications and the efficacy of ICT.

Patients and methods

Overall population

We reviewed the database of all NSCLC patients who underwent ICT followed by a surgical resection from January 1980 to December 2009 at the Georges Pompidou European Hospital (GPEH), Paris, or the Cedar Surgical Centre, Bois Guillaume, where a part of the GPEH medical team was relocated.

A Cancer Multi-Disciplinary Team (MDT) formed in 1975 discussed all cases during thoracic Tumor Board Conferences (TBCs).[16] The MDT decided, according to the American Society of Clinical Oncology and the American Association for Thoracic Surgery, whether patients should receive ICT and whether surgery should be offered after surgery. Resectability criteria did not change over time.

Preoperative workup

The data were prospectively entered from April 1984. Before 1984, the preoperative workup included chest X-ray, bronchoscopy, spirometry, and hepatic ultrasound. In addition, a computed tomography scan (CT) of the chest, upper abdomen, and brain, and a lung-perfusion scan have been performed since 1983, and a fluoro-deoxyglucose-positron emission tomography (FDG-PET) scan was added to this workup in 2004.

Before the PET scan was available, the diagnosis of clinical N2 diagnosis was based on CT scan LN size only; after 2004, a decision to biopsy mediastinal LNs was made when nodes were found to be larger than 1 cm in the shortest transverse axis on chest CT scan or positive on FDG-PET scan.

Pathological and molecular assessment

In 2009, the World Health Organization (WHO) and the new International Staging System for NSCLC reclassified the criteria for lung tumors.[12,17]

Since 2009, in adenocarcinomas and mixed lung cancers with an adenocarcinoma component, resected tumors are tested for epidermal growth factor receptor (EGFR) mutation in case of node involvement. In cases of EGFR activating mutation, patients are selected for EGFR-targeted tyrosine kinase inhibitor treatment if they have locally advanced or metastatic tumors.

Induction chemotherapy indications

Salvage lung resection was defined as a surgery following curative-intent chemoradiation therapy. Operability refers to the patients' ability to cope with both the operation and the subsequent reduction of lung volume and function. Borderline operability was defined as a level of fitness that could lead to a greater than average morbidity or mortality from surgery, that is, a predicted postoperative forced expiratory volume in one second of 35%, according to the European Respiratory Society and the European Society of Thoracic Surgery.[18] Borderline resectability was defined by the risk of exploratory thoracotomy without resection.

Response

Clinical mediastinal LNs with a diameter of 10 mm or more on CT scan were considered abnormal. N2 were divided into "clinical" and "bulky." Bulky disease was defined as LNs >2 cm in the short-axis diameter on chest CT, disease in a group of LNs, or involvement of more than two LN stations [http://www.cancernetwork.com/oncology-journal/managing-patient-borderline-resectable-lung-cance].

Pathologic staging of the mediastinum was performed prior to and within three weeks of induction therapy, when LNs were accessible.

N2 patients were defined as patients with positive mediastinoscopy or positive PET and CT scans. Some patients whose disease was staged N2 by CT only were also included: patients with N2 involvement on specimen examination and patients with bulky N2 at CT scan and/or mutiple station involvement.[19]

Clinicians and a staff member in thoracic radiology assessed radiologic response, by comparing the bidimensionally measurable lesions on a thoracic CT scan before and two to four weeks after the last chemotherapy. According to WHO criteria, complete response (CR) was defined as the disappearance of all measurable disease and the absence of new lesions, and partial response (PR) was defined as a reduction of > 30% of the sum of the products of the cross-sectional diameters of all measurable lesions and the absence of new lesions.[20] Stable disease (SD) was defined as a <20% reduction of the sum of the products of the cross-sectional diameters of all measurable lesions and the absence of new lesions, and progressive disease (PD) was defined as a > 20% increase in the sum of the products of the cross-sectional diameters of all measurable lesions or the appearance of new lesions. The sum of the CR plus the PR was defined as overall clinical response.

Clinical LN downstaging was defined as the disappearance (i.e. reduced size to below 1 cm) of enlarged mediastinal LNs at CT scan.

A pathologic response evaluation was performed by determination of the proportion of necrotic and/or fibrotic material using surgical resection specimens. A pathologic CR was defined as the absence of malignant cells at pathologic examination after preoperative treatment. A complete surgical resection was defined as a tumor with free margins and negative highest mediastinal LNs. Our thoracic surgery society ethics committee approved the study and waived the need for informed consent.

Toxicity

Toxicities induced by preoperative chemotherapy and chemoradiation therapy were assessed by means of WHO criteria. Toxicity was assessed at the end of each cycle of chemotherapy, and hematologic assessment was performed weekly. The poorest data for each patient in all cycles of chemotherapy were used in toxicity analysis.

Surgery

During the three consecutive periods of our study, patients underwent the same surgical protocol according to international recommendations.[21,22] Until today, lobectomy associated with radical complete mediastinal LN dissection has represented the gold standard for localized NSCLC treatment, particularly in stages I and II.[22,23] Indeed, to date there has been no randomized trial demonstrating the benefit for infra lobar resection. In extended local invasion, pneumonetomy must be proposed to obtain R0 status. For stage IIIA N2, two different situations may be differentiated. In limited LN involvement there is no formal consensus and in our department patients with discrete single chain N2 involvement preoperatively identified (IIIA) received primary surgical resection followed by adjuvant therapy. In cases of larger LN involvement, neoadjuvant chemotherapy was preferred.[24,25] Adjuvant therapy was decided according to final histological analysis.

Study design

We focused on patients who underwent ICT. We analyzed indications, tolerance, and efficacy of ICT, comparing three periods of nine years: 1980–1989, 1990–1999, and 2000–2009. We defined three study periods corresponding to major strategic changes improving tumor node metastasis (TNM) evaluation: routine use of tomodensitometry (TDM) during the second period, and PET-TDM and exploratory VATS during the third period.

Follow-up data

Follow-up information was obtained from hospital case records, a questionnaire completed by the chest physician or the general practitioner, or from death certificates. We defined overall survival (OS) as the time interval between the date of the surgery and the date of the death or last follow-up visit for censored patients. Mortality was defined as 30-day mortality. Cancer-specific survival (C-SS) was calculated as the period from the date of surgery until the date of first recurrence, loco-regional or systemic.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median (range); categorical variables were described as count (proportion). OS was estimated using the Kaplan–Meier method. Comparisons between groups were performed using the Wilcoxon rank sum test for continuous variables, the χ^2 or Fisher's exact test for categoric variables, and the log-rank test for OS. The predictive or prognostic impact of certain variables was investigated using the Cox proportional hazards model for OS. The association of OS with main individual factors was assessed in univariate analysis including: age, gender, smoker status, histology, tumor stage, LN involvement, induction treatment, clinical response, surgical procedure, clinical mediastinal downstaging, and complete resection. The prognostic impact of ICT on survival was also investigated in multivariate analyses including clinical responses, clinical mediastinal downstaging, and complete resection. All tests were two-sided, and a *P*-value of <0.05 was considered significant. The statistical software SEM (Anticancer Centre Jean Perrin, Clermont-Ferrand, France) was used for analysis.[26]

Results

Patient characteristics

A total of 732 patients referred by four university and five non-university hospitals underwent surgical resection of NSCLC following ICT between January 1980 and 2009.

The main clinical and pathological characteristics included a majority of men (80.74%), a mean age of 59.8 years (median 60, range 30–81), a majority with a smoking history (95%), and squamous cell carcinoma (50.6%).

Clinical stages were: stage I in 88 (12.02%), stage II in 82 (11.2%), stage IIIA in 387 (58.87%), stage IIIB in 99 (13.52%), and stage IV in 76 patients (10.38%). Patients diagnosed with stage IIIA NSCLC fell into three groups: patients with T3 N1 (n = 95, 25%); with clinical N2 disease diagnosed preoperatively, with imaging or surgical procedures (n = 260, 67% including 52 patients diagnosed by mediastinoscopy); and patients with multiple station bulky-N2 involvement (n = 32; 4.37%). All stage IIIB patients presented T4N2 tumors.

All stage IV-patients were operated on for their metastasis before lung surgery. Each case had brain metastasis resected to diagnose primitive tumor.

The evolution of patient characteristics over time is summarized in Table 1, and included a decreasing frequency of male patients, squamous cell carcinoma, and stage IIIB disease.

Indications of ICT included: clinical N2 (n = 260, 35.52%); assessment of oncologic operability (n = 187, 25.5%); oligometastases (n = 60, 8.2%); phase III trial (n = 52, 7.1%); clinical bulky N2 (n = 32, 4.37%); limited pulmonary volumes and/or diffusing capacity of the lungs for carbon monoxide requiring parenchyma-sparing resection by sleeve, segmentectomy or wedge (n = 34; 4.64%); and salvage surgery (n = 14, 1.91%). Miscellanous reasons (n = 88, 12.02%) consisted of a patient's initial refusal for surgery, poor pulmonary function, major bronchorrhea requiring preoperative rehabilitation, and coated coronary stenting requiring double anti platelet therapy. Five indications (0.68%) were not available. ICT was proposed in 34 patients with limited pulmonary volumes and/or diffusing capacity of the lungs for carbon monoxide in order to achieve smoking cessation and pulmonary rehabilitation.

The evolution of indication over time revealed an increasing frequency of N2 disease and a decreasing frequency of unresectable tumors, as shown in Table 2.

Indications of adjuvant chemotherapy

Between 1980 and 2004, patients underwent adjuvant chemotherapy in case of N2 involvement, oligometastases, and inclusion in phase trial. From 2004–2008, patients in stage IB, II, III, IV, and after 2008 patients in stage IB with tumor size ≥4 cm, stage II, IIIA, and IV disease, also underwent adjuvant chemotherapy in case of N2 involvement, oligometastases, and inclusion in phase trial (Table 3).

Regimen

Chemotherapy consisted of an association of drugs in 720 cases and included platinum in 669 cases (91.39%). The chemotherapy regimen consisted of an association of: platinum and placlitaxel or docetaxel (n = 191; 26.09%); platinum and gemcitabine (n = 163, 22%); platinum and vinorelbine (n = 160; 21.86%); mitomycin-ifosfamide-platinum (n = 120; 16.39%); platinum and 5 Fluorouracil (n = 67; 9.15%); platinum and etoposide (n = 27; 3.69%); or platinum and pemetrexed (n = 4; 0.55%). No patient received EGFR tyrosine kinase inhibitors. Time evolution showed a cessation in the use of platinum-5 Fluororacil after 1989 and mitomycin-ifosfamide-platinum after 1999.

Table 1 Evolution of main clinical and pathological characteristics over time

Variable	1980–1989 (n = 35)	1990–1999 (n = 274)	2000–2009 (n = 423)	Total (n = 732)	*P* value
Demographics					
Male	32 (91.43%)	230 (83.94%)	329 (77.78%)	591 (80.74%)	0.033
Age: median (range)	61.3 (45–78)	59.4 (30–77)	60 (30–81)	60 (30–81)	0.41
Histology					
Squamous cell	22 (62.86%)	157 (57.3%)	182 (43.03%)	361 (49.32%)	0.00038
Adenocarcinoma	6 (17.14%)	58 (21.17%)	177 (41.84%)	241 (32.92%)	$<10^{-6}$
Large cell	1 (2.86%)	29 (10.58%)	44 (10.4%)	74 (10.11%)	0.35
Others	0 (0%)	2 (0.73%)	3 (0.71%)	5 (0.68%)	0.88
Clinical staging					
Stage I	5 (14.29%)	31 (11.31%)	52 (12.29%)	88 (12.02%)	0.85
Stage II	9 (25.71%)	22 (8.03%)	51 (12.06%)	82 (11.2%)	0.0054
Stage IIIA	13 (37.14%)	150 (54.74%)	224 (52.96%)	387 (58.87%)	0.14
Stage IIIB	4 (11.43%)	49 (17.88%)	46 (10.87%)	99 (13.52%)	0.028
Stage IV	4 (11.43%)	22 (8.03%)	50 (11.82%)	76 (10.38%)	0.12

Table 2 Evolution of induction chemotherapy indications over time

Variable	1980–1989 (n = 35)	1990–1999 (n = 274)	2000–2009 (n = 423)	Total (n = 732)	*P* value
Clinical trial	0 (0%)	16 (5.84%)	36 (8.51%)	52 (7.1%)	0.098
Clinical N2	8 (22.86%)	88 (32.12%)	167 (39.48%)	260 (35.52%)	0.035
Bulky N2	0 (0%)	13 (4.74%)	24 (5.67%)	32 (4.37%)	0.32
Limited pulmonary function	1 (2.86%)	8 (2,92%)	25 (5,91%)	34 (4,64%)	0.16
Oligo-metastases	4 (11.43%)	14 (5.11%)	42 (9.93%)	60 (8.2%)	0.058
Unresectable tumor	11 (31.43%)	104 (37.96%)	72 (17.02%)	187 (25.55%)	$<10^{-6}$
Salvage surgery	0 (0%)	4 (1.46%)	10 (2.36%)	14 (1.91%)	0.49
Not available	1 (2.86%)	1 (0.36%)	3 (0.71%)	5 (0.68%)	0.24
Others	10 (28.57%)	26 (9.49%)	52 (12.29%)	88 (12.02%)	0.0048

Table 3 Efficacy of induction therapy and type of resection over time

Variable	1980–89 (n = 35)	1990–99 (n = 274)	2000–09 (n = 423)	Total (n = 732)	*P*-value
Clinical response to chemotherapy					
Complete response	2 (5.71%)	14 (5.11%)	13 (3.07%)	29 (3.96%)	0.35
Partial response	16 (45.71%)	187 (68.25)	286 (67.61%)	489 (66,8%)	0.024
Stable disease	15 (42.86%)	64 (23.36%)	85 (20.09%)	164 (22.4%)	0.0073
Progression	2 (5.71%)	4 (1.46%)	12 (2.84%)	18 (2.46%)	0.024
Not available	0	5 (1.82%)	27 (6.38%)	32 (4.37%)	0.0071
Type of resection					
Lobectomy	10 (28.57%)	66 (24.09%)	167 (39.48)	243 (33.2%)	0.00017
Wedge	0 (0%)	5 (1.82%)	13 (3.07%)	18 (2.46%)	
Segment	1 (2.86%)	2 (0.73%)	6 (1.42%)	9 (1.23%)	0.00014
Bilobectomy	2 (5.71%)	8 (2.92%)	17 (4.02%)	27 (3.69%)	
Sleeve lobectomy	2 (5.71%)	14 (5.11%)	28 (6.62%)	44 (6.01%)	
Pneumonectomy	20 (57.14%)	161 (58.76%)	184 (43.5%)	365 (49.86%)	0.00038
Completion	0 (0%)	3 (1.09%)	5 (1.18%)	8 (1.09%)	
Resection					
R0	29 (82.86%)	213 (77.74%)	338 (79.91%)	580 (79.23%)	0.69
R1	2 (5.71%)	23 (8.39%)	37 (8.75%)	62 (8.47%)	0.83
R2	3 (8.57%)	23 (8.39%)	45 (10.64%)	71 (9.7%)	0.0.26
ET	0 (0%)	15 (5.47%)	3 (0.71%)	19 (2.6%)	0.00019
Pathologic stage					
0	3 (8.57%)	13 (4.74%)	27 (6.38%)	43 (5.87%)	0.53
IA	2 (5.71%)	24 (8.76%)	47 (10.98%)	73 (9.97%)	0.33
IB	7 (20%)	23 (8.39%)	44 (10.4%)	74 (10.11%)	0.33
IIA	2 (5.71%)	34 (12.41%)	53 (12.53%)	89 (12.16%)	0.79
IIB	4 (11.43%)	24 (8.76%)	42 (9.93%)	70 (9.56%)	0.79
IIIA	11 (31.43%)	110 (40.15%)	165 (39.01%)	286 (39.07%)	0.50
IIIB	2 (5.71%)	10 (3.65%)	11 (2.6%)	23 (3.14%)	0.47
IV	4 (11.43%)	21 (7.66%)	31 (7.33%)	56 (7.65%)	0.66
Pathologic CR	2 (5.71%)	22 (8.03%)	39 (9.22%)	63 (8.61%)	0.0000013
Adjuvant treatment					
No adjuvant therapy	19 (54.29%)	103 (37.59%)	206 (48.7%)	328 (44.81%)	
Adjuvant therapy:	16 (45.71%)	171 (62.41%)	217 (51.3%)	404 (55.19%)	0.0071
Radiotherapy	13 (37.14%)	110 (40.15%)	94 (22.22%)	217 (29.64%)	
Chemotherapy	2 (5.71%)	26 (9.49%)	72 (17.02%)	100 (13.66%)	0.00004
Chemo and radiation therapy	1 (2.86%)	35 (12.77%)	51 (12.06%)	87 (11.89%)	

The number of patients who did not receive adjuvant treatment included 27 postoperative deaths and 63 palliative-chemotherapy. CR, complete response; ET, exploratory thoracotomy.

The median number of cycles was two (range 1–6); 14 patients (2%) failed to complete the ICT course. Severe toxicity decreased over time from 14.6% to 11.5%, without achieving a significant difference ($P = 0.24$).

Response rate

The clinical response rate, surgical management, and pathological results are summarized in Table 3. The overall response rate for 700 evaluated patients was 29 CR (3.96%), 489 PR (66.8%), 164 SD (22.4%), and 18 PD (2.46%) (Figure 1).

The evolution of response rate over time showed an increased proportion of PR and a decreased proportion of SD between the first and second periods, but no significant change since then. There were no significant associations between clinical response and patients' age, gender, smoking habits, histology, stage, and LN involvement.

Surgical resection

As shown in Table 3, pneumonectomy was performed in 365 (49.86%), bilobectomy in 27 (3.69%), lobectomy in 243 (33.2%), and sleeve lobectomy in 44 patients (6.01%). Complete resection was achieved in 580 patients (79.23%). Postoperative complications and deaths occurred in 145 (19.8%) and 27 (3.7%) patients, respectively.

A total of 329 patients (44.95%) received adjuvant treatment including radiotherapy (n = 217; 29.64%), chemotherapy (n = 100, 13.66%), or both (n = 87, 11.89%).

Survival

Median follow-up of the living patients was 75 months. As of the index date of the 15 January 2013, 197 patients (26.9%) were alive, including 183 patients (25%) without evidence of disease. Three hundred and thirty-six patients had died from lung cancer, and 121 had died from causes other than lung cancer. The cause of death was unknown in 79 cases. The five and 10-year overall survival rates were 35.2% and 21.5% for the study population, and 42.5% and 26.2% in case of R0 resection, respectively. The rate of 30-day mortality was 6.2% after pneumonectonectomy (right lung: 3%, left lung: 2%) and 2.8% after lobectomy (right lung: 9.1%, left lung: 3.3%). The five-year C-SS and OS rates were 37.1% and 34.9%, respectively.

Prognostic analyses

In univariate analysis, patients presenting CR or PR to chemotherapy had better survival rates. Patients with respiratory

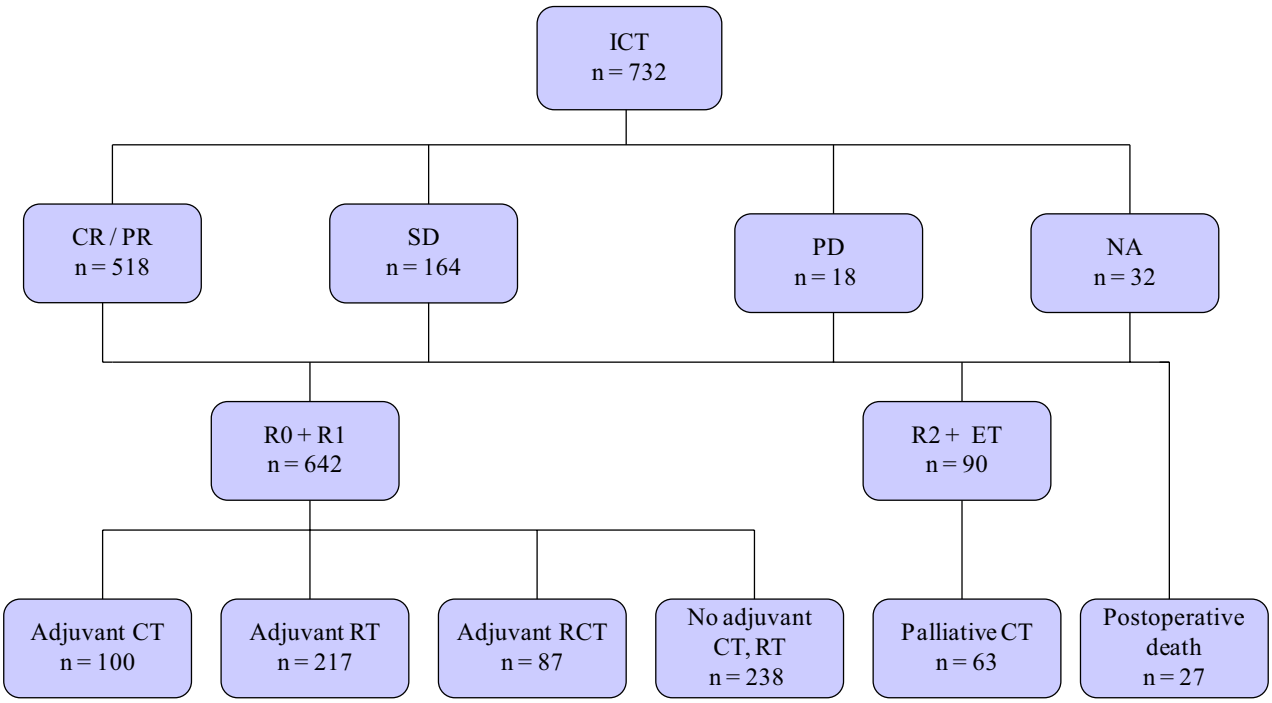

Figure 1 Flow chart. The overall clinical response rate (ORR) for 700 evaluated patients was: 29 complete response (CR, 3.96%), 489 partial response (PR, 66.8%), 164 stable disease (SD, 22.4%), and 18 progressive disease (PD, 2.46%).CT, chemotherapy; ICT, induction chemotherapy; NA, not available; R0, microscopic complete resection; R1, microscopic incomplete resection; R2, macroscopic incomplete resection; RT, radiotherapy; RCT, radiochemotherapy.

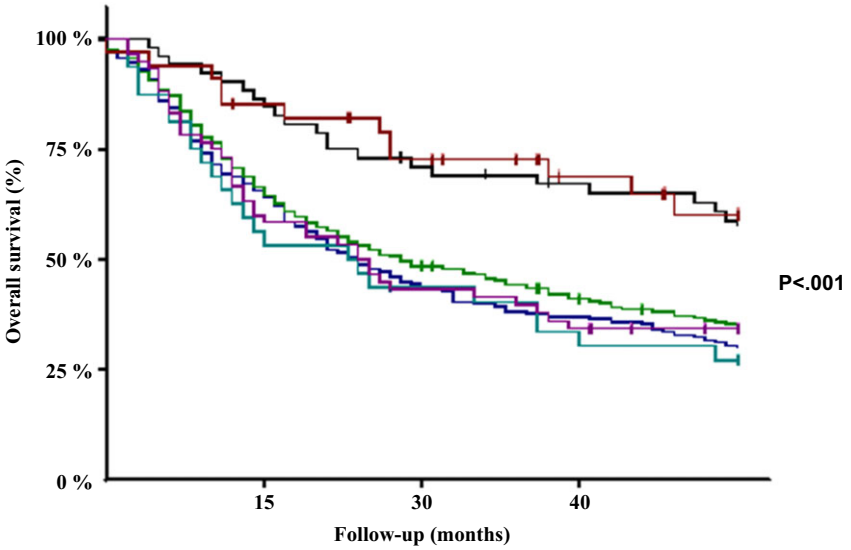

Figure 2 Survival by indications of induction chemotherapy. Patients with limited respiratory pulmonary volumes and/or diffusing capacity of the lungs for carbon monoxide requiring parenchyma-sparing resection; patients included in clinical randomized trials had better survival than other indications for induction therapy ($P < 0.001$). ——, Phase 3 trials; ——, Respiratory function; ——, Metastases; ——, Clinical N2; ——, Unresectability; ——, Bulky N2.

failure requiring parenchyma-sparing resection, and for those included in a clinical randomized trial had better survival than other indications for induction therapy ($P < 0.001$), as shown in Figure 2. Multivariate analysis identified time period, age, clinical response to chemotherapy, type of resection, and pathological LN involvement as strong prognostic factors of OS. The results of multivariate analysis are summarized in Table 4.

Table 4 Multivariate analysis of survival

Variable	HR	95% CI	*P* value
Age:			0.00052
>60 vs. ≤60	1.41	1.18–1.69	
Type of resection:			0.000043
Exploratory thoracotomy vs. lobectomy + segmentectomy	2.12	1.48–3.03	
Pneumonectomy vs. lobectomy + segmentectomy	1.45	1.22–1.74	
Histology:			0.000078
ADC vs. SCC	1.28	1.13–1.45	
Others vs. SCC	1.65	1.29–211	
Overall response to ICT:			0.0017
No vs. yes	1.41	1.18–1.69	
Time-period			0.0037
1990–99 vs. 2000–09	1.18	1.01–1.37	
1980–89 vs. 1990–99	1.38	1.02–1.88	

ADC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; ICT, induction chemotherapy; SCC, squamous cell carcinoma.

Discussion

Clinical response rate increased over the 30-year study, supporting ICT use. However, while progress was made during the 1990's, no major advance has been made since then. Similarly, the rate of pathologic CR improved very slowly, and very few prospective clinical trials evaluating ICT have recently been conducted (http://www.clinicaltrials.gov). These findings suggest that more trials should focus on selecting the best candidates for induction therapy through the identification of biomarkers from initial tumor biopsy in order to adapt the induction strategy.

This study summarized the 30-year experience of ICT and surgery in a cohort of patients referred by nine different centers to a single surgical team. Questioning the evolution of ICT in a surgical practice, we found: (i) the frequency of ICT use had increased, with a rising proportion of clinical N2 and a declining proportion of initially unresectable disease; (ii) the efficacy of ICT improved, with a higher rate of PR after 1990 (P2), but no significant change since then (P3); and (iii) ICT results were better when patients were included in phase 3 clinical trials.

Frequency of induction therapy

This study highlights the increasing use of ICT during the last 30 years, with a frequency rising from 3% in the 1980's to 20% in the years since 2000. Strikingly, ICT is mainly utilized for patients with very poor prognoses. N2 involvement and borderline resectability represent two-thirds of the cases in which

ICT is utilized. However, the increasing use of ICT has progressively focused on N2 disease, which is a well-accepted strategy in European centres today, even though more data are required. The decrease in initially unresectable disease, mainly in stage II patients, is probably partly explained by stage migration. We noted that a large number of patients with clinical stage I disease underwent ICT and resection. This could be explained by the enrollment of stage I-II patients in clinical trials testing ICT, but could also be attributed to the puzzling data found in the literature regarding chemotherapy efficacy in early NSCLC disease. Adjuvant chemotherapy is now accepted on the basis of randomized clinical trials and meta-analysis that demonstrated improved survival in patients with pathological stage IB $\geq$ 4 cm.[5,9] However, to date, the stage-adjusted benefit of preoperative chemotherapy, and indications in comparison with adjuvant chemotherapy in stages IB and II, remain questioned. To date, several randomised trials have failed to demonstrate a significant survival benefit from the addition of preoperative chemotherapy.[8,10,14,27]

Efficacy of induction therapy

Whatever the indications, the ICT benefit seems to be the same: high rates of clinical response (74%) and complete pathologic response (9.2%) were found following ICT during the last decade.[28,29]

Response to chemotherapy was associated with a complete resection in 79.2% patients with a five-year OS of 42.5% in this subgroup. In addition, even if pneumonectomy was frequent (49.86%) for these large and aggressive tumors, the postoperative complication (19.8%) and mortality rates (3.7%) were both acceptable.

However, the difference between OS (34.9%) and C-SS (37.1%) rates underlines the high rate of mortality related to causes other than lung cancer. Indeed, the cohort had a median age of 60, and the study included patients from over 30 years ago.

Patients included in the clinical trial

Strikingly, we found significantly improved outcomes in phase III trials (7% of patients) over standard therapy. Naturally, experimental treatment may offer a superior therapeutic effect, but other reasons are complex to analyse. Patients with advanced disease were not eligible, therefore, were not included in the trial. In addition, differences in patients' baseline characteristics inducing a selection bias have also been described, with the inclusion of patients of higher socioeconomic status, younger age, and earlier stage in clinical trials compared with the overall cancer population.[30] Finally, some authors identified a trial or participation effect. Such an effect exists when participants in the control group perform better than individuals who were not enrolled in a clinical trial.[31] Braunholtz *et al*. explained the trial effect as including: a protocol effect, that is, the result of following detailed and rigid guidelines; a care effect, that is, the result of extra follow-up and nursing care; the Hawthorne effect, that is, the change in patient-physician relationship as a result of both being observed; and the well-known placebo effect.[32]

Limitations of the study

Our results must be analyzed considering several biases resulting from the long accrual period, in particular, the evolution of pretreatment evaluation, and chemotherapy regimens. In addition, there were several confounding variables between the three time periods (significant differences in clinical and demographic characteristics, indications for ICT, pathology, surgical radicality, and adjuvant therapy), which caused complexity in the comparison. However, our study outlines the importance of additional: (i) real-life studies reporting the outcome of NSCLC patients following TBCs decisions and standard of care therapy, and (ii) large-scaled studies analyzing population-based cancer registries.

Conclusion

The evolution of daily practice during the last 30 years demonstrates an increased use of ICT, a progressive focus on N2 disease, and improved response rates. This changing pattern of medical practice is associated with good tolerance, high rates of complete resection, and 37.1% five-year C-SS. The respective positions of induction and adjuvant therapies, together with the best chemotherapy regimen, must still be established.

Disclosure

No authors report any conflict of interest.

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