Non-small-cell lung cancer in a French department, (1982–1997): management and outcome

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Addition of chemotherapy to the treatment of non-small-cell lung cancer (NSCLC) resulted in a modest but clear improvement in the survival of selected patients. To ascertain if this translates to improved survival in the whole population of patients, we conducted a retrospective population-based study of a sample of 1738 patients diagnosed with primary NSCLC in a French department between 1982 and 1997. The proportion of women, metastatic cases and adenocarcinoma changed significantly over time, as did their management: use of chemotherapy alone increased from 9.7 to 28.1% (P<0.0001), while the use of radiotherapy alone decreased from 32.2 to 9.4% (P<0.0001). The 5-year survival probability was 15.7% for all patients and 32.6% for those with resectable disease. The 1- and 2-year survival probabilities were 38.2 and 15.6% in locally advanced disease, and were, respectively, 16.8 and 5.2% in metastatic disease. Disease extent and histological subtype were significant independent prognostic factors. Survival of resectable disease was longer among patients treated with surgery or surgery plus chemotherapy, while better outcomes for locally advanced disease were associated with radiation plus chemotherapy. In metastatic disease, patients treated by classical agent without platin or palliative care only had the shortest survival. Despite changes in treatment in accordance with the state-of-the-art, overall survival did not improve over time. It is not unlikely that more patients with bad PS were diagnosed during the latter end of the study period. This could at least partially explain the absence of detection of an overall improvement in survival.

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Lung cancer, one of the most common malignancies, is the leading cause of cancer death among men throughout the industrialised world (Ferlay et al, 2001). Since 1987, lung cancer has caused more deaths than breast cancer among North American women (US Public Health Service, 2001), and it is now the third leading cause of cancer deaths among French women (Hill and Doyon, 2004).

Non-small-cell lung cancer accounts for approximately 75% of all lung cancers. Its prognosis is poor: 5-year survival rates range from 60% in resected stage IA disease to 5% in stage IIIB and 1% in stage IV (Mountain, 1997). At diagnosis, approximately 75% of patients have tumours classified as stage III or IV disease (Fry et al, 1999). Management of Non-small-cell lung cancer (NSCLC) has changed substantially over the past two decades with an increasing use of chemotherapy. At the beginning of the 1980s, the standard treatments were surgery for resectable tumours, mediastinal irradiation for locally advanced disease and supportive care for metastatic disease. Meta-analyses (Souquet et al, 1993; NSCLCCG, 1995) of the clinical trials comparing chemotherapy vs no chemotherapy report modest but clear improvement in survival for patients with metastatic or locally advanced disease who are treated with cisplatin-based chemotherapy and a trend towards improved survival with adjuvant chemotherapy in resectable disease. (The favourable impact of adjuvant chemotherapy has just been demonstrated very recently; The IALT Collaborative Group, 2004). Preoperative chemotherapy strategies might improve survival in resectable stage IIIA disease (Roth et al, 1994) as well as in stages I and II (Depierre et al, 2002).

To evaluate the effect on survival of these management changes in a population-based study, we conducted a retrospective study over a 16-year period of a sample of 1738 patients diagnosed with NSCLC in the department of Bas-Rhin (northeastern France).

PATIENTS AND METHODS

Patients

The Bas-Rhin population-based cancer registry furnished us with a list of patients with confirmed NSCLC. This department had a population of roughly 1 000 000 inhabitants during the study period (INSEE, 1982, 1990, 1999). We included 40% of the 5071 cases diagnosed between 1982 and 1997 and randomly selected 2028 patients, stratified by year of diagnosis.

We reviewed the medical records of each patient and excluded those with in situ carcinoma or a combination of small-cell and NSCLC. The following data were collected: age, sex, date of diagnosis, histological subtype, investigations performed for diagnostic and staging purposes and disease extent. We did not attempt to assign stages retrospectively but used the stage assigned by the patient’s physician at diagnosis: resectable disease, locally...
advanced unresectable disease and metastatic disease. The stage was classified as undetermined if the chart did not report the local extent of the disease at diagnosis and if no metastatic site was detected.

Initial treatment (surgery, radiotherapy, chemotherapy, palliative care) and any clinical trial participation were also recorded. Chemotherapy was divided into classical agents and more recent agents (vinorelbine, gemcitabine, irinotecan) and subdivided into protocol with or without platin.

Survival was estimated from the date of pathological diagnosis. The end of follow-up was 31 December 2002.

Statistical methods

Descriptive analysis We defined four consecutive periods covering 4 years each. Differences between proportions were assessed with either Pearson’s $\chi^2$ test or Fisher’s exact test. Differences between the means of continuous variables were evaluated with Student’s $t$-test or, if the comparison involved more than two groups, one-way analysis of variance. The 8.2 SAS software package (SAS Institute, Cary, NC, USA) was used to analyse the data.

Survival analysis Our study covered 16 years. To eliminate the effect of improved survival for the other pathologies and the effect of age-related mortality, we conducted simple and multiple regressive analysis of relative rather than crude survival (Esteve et al., 1990) with the RELSURV software package (Hédelin, 2003). The variables with a $P$-value of 0.20 or less in the simple regressive analysis were entered in the multiple regressive analysis. Sex and period were forced in the model. The proportionality assumption has been verified using interaction with time. Interactions between variables were tested, and none was statistically significant.

Power considerations Our principal objective was to determine whether relative survival globally changed in NSCLC patients between 1982 and 1997. Using registry data, we estimated that the 5-year relative survival rate was 15% in the early 1980s, and we wanted to be able to detect an increase of at least five points, that is, a 5-year relative survival rate of 20% at the end of the 1990s under the assumption of the proportionality of the risks. With the formula given in Jung and Hui (2002) and assuming a one-sided test with an alpha level of 0.05 and a power of 0.80, we estimated that a sample size of 490 patients would be required in each of the four periods.

RESULTS

Descriptive analysis

We excluded 290 of the 2028 patients randomly selected from the registry: 197 patients had missing medical records, and 93 did not meet the inclusion criteria. The study thus included 1738 patients, 89.8% of the 1935 eligible.

Table 1 summarises the patients’ characteristics and their trends over time.

| Period     | 1982–85 | 1986–89 | 1990–93 | 1994–97 |
|------------|---------|---------|---------|---------|
|            | No. %   | No. %   | No. %   | No. %   |
| Sex        |         |         |         |         |
| Male       | 319 91.4 | 380 89.4 | 411 87.6 | 431 87.1 |
| Female     | 30  8.6  | 45  10.6 | 58  12.4 | 64  12.9 |
| Age (years)|         |         |         |         |
| ≤55        | 82  23.5 | 101  23.8 | 93  19.8 | 108 21.8 |
| 56–70      | 144 41.3 | 210  49.4 | 255 54.4 | 268 54.1 |
| >70        | 123 35.2 | 114  26.8 | 121 25.8 | 119 24.0 |
| Treatment on protocol | 11 3.2 | 6 1.4 | 20 4.3 | 36  7.3 |
| Disease extent |         |         |         |         |
| Resectable | 182 52.1 | 197 46.4 | 204 43.5 | 202 40.8 |
| Locally advanced | 52 14.9 | 70 16.5 | 96 20.5 | 94 19.0 |
| Bilateral  | 7  2.0   | 13  2.9  | 6  1.3   | 12  2.4 |
| Metastatic | 92 26.4  | 126 29.6 | 149 31.8 | 174 35.2 |
| Undetermined | 16 4.6 | 19  4.5 | 14  3.0  | 13  2.6 |
| Histology   |         |         |         |         |
| Squamous-cell | 229 65.6| 282 66.4| 300 64.0| 267 53.9|
| Adenocarcinoma | 69 19.8 | 92 21.6 | 100 21.3 | 148 29.9|
| Bronchioloalveolar | 13  3.7 | 16  3.8 | 26  5.5 | 18  3.6|
| Large-cell  | 35 10.0  | 34  8.0  | 41  8.7  | 51 10.3|
| Mixed      | 3  0.9   | 1  0.2   | 2  0.4   | 11  2.2 |

*Linear trend significant.
From period 1 through period 4, the mean number of metastatic sites detected increased from 0.36 to 0.57 ($P = 0.0057$) and the mean number of extra-thoracic imaging procedures from 1.79 to 2.87 ($P < 0.0001$). These increases were significantly correlated ($r = 0.13$, $P < 0.0001$).

In all, 17 cases discovered incidentally at autopsy or who died before diagnosis were excluded from the following analyses.

Treatments for each stage differed significantly from the first to the last study period ($P < 0.0001$, Table 3). Data for cases involving bilateral disease and undetermined stage are not shown. The percentage of patients treated with mediastinal irradiation alone decreased over time from 32.2 to 9.4% ($P < 0.0001$) for every stage. On the other hand, the combined use of chemo- and radiotherapy increased significantly over time for the locally advanced stage and the use of chemotherapy alone increased significantly from 9.7 to 28.1% ($P < 0.0001$), especially for metastatic disease. The use of surgery alone for resectable disease increased over the study period, while the use of surgery plus radiotherapy did not change. Of the patients in this group, 73.0% had tumours resected: 64.1% with pTNM stage I or II, 25.2% stage IIIA and 8.6% stage IIIB or IV (2.1% unknown).

Chemotherapy used a single agent in 11.7% of the cases, two in 39.5%, three in 17.8% and four or more in 31.0%. Cisplatin was one of the drugs in 81.4% of the cases. The drugs used changed significantly over time: use of vindesine, cyclophosphamide and lomustine decreased significantly after 1986, while use of vinorelbine, ifosfamide and mitomycin-C increased significantly from 1986. The principal regimen during the first two periods was

### Table 2 Imaging procedures performed during the study period

| Period   | 1982–85 |  | 1986–89 |  | 1990–93 |  | 1994–97 |  |
|----------|---------| |---------| |---------| |---------| | 
|          | No. | %     | No. | %     | No. | %     | No. | %     | P   |
| Fibrescopy | 336 | 96.6 | 412 | 97.4 | 454 | 97.8 | 474 | 96.3 | 0.4999 |
| Thoracic-CT scan* | 72 | 20.7 | 177 | 42.0 | 402 | 86.8 | 472 | 96.3 | <0.0001 |
| Thoracic NMR* | 10 | 2.4 | 12 | 2.6 | 12 | 2.6 | 11 | 2.3 | 0.9501 |
| Abdominal US | 321 | 92.8 | 376 | 90.4 | 425 | 92.6 | 425 | 89.3 | 0.1973 |
| Adrenal CT scan* | 18 | 5.2 | 83 | 20.0 | 220 | 48.1 | 245 | 51.6 | <0.0001 |
| Abdominal CT scan* | 12 | 3.5 | 30 | 7.2 | 82 | 17.9 | 134 | 28.1 | <0.0001 |
| Brain CT* | 33 | 9.6 | 160 | 38.5 | 313 | 67.7 | 386 | 80.9 | <0.0001 |
| Bone scan* | 171 | 49.4 | 175 | 42.1 | 212 | 46.4 | 275 | 57.8 | <0.0001 |
| Brain scan* | 67 | 19.4 | 16 | 3.9 | 0 | 0.0 | 0 | 0.0 | <0.0001 |
| Brain NMR* | 1 | 0.3 | 3 | 0.7 | 7 | 1.5 | 10 | 2.1 | 0.0823 |
| Mediastinoscopy | 2 | 0.6 | 4 | 1.0 | 6 | 1.3 | 5 | 1.0 | 0.8181 |
| Other | 35 | 10.1 | 34 | 8.2 | 41 | 9.0 | 37 | 7.8 | 0.6643 |

*Linear trend significant. $^a$2 calculated from 1986. CT: computed tomography; US: ultrasound; NMR: nuclear magnetic resonance imaging.

### Table 3 Therapeutic management over time

| Period   | 1982–85 |  | 1986–89 |  | 1990–93 |  | 1994–97 |  |
|----------|---------| |---------| |---------| |---------| | 
|          | No. | %     | No. | %     | No. | %     | No. | %     | P   |
| Resectable disease | | | | | | | | |
| Radiotherapya | 44 | 24.4 | 35 | 17.9 | 26 | 12.7 | 23 | 11.4 | 0.0023 |
| Surgery* | 60 | 33.3 | 99 | 50.5 | 108 | 52.9 | 112 | 55.4 | <0.0001 |
| Chemotherapy | 2 | 1.1 | 2 | 1.0 | 5 | 2.5 | 6 | 3.0 | 0.4290 |
| Surgery+radiotherapy | 31 | 17.2 | 41 | 20.9 | 34 | 16.7 | 24 | 11.9 | 0.1149 |
| Surgery+chemotherapy | 11 | 6.1 | 5 | 2.6 | 6 | 2.9 | 8 | 4.0 | 0.2777 |
| Chemotherapy+radiotherapy | 13 | 7.2 | 1 | 0.5 | 2 | 1.0 | 8 | 4.0 | 0.0004 |
| Surgery+radio+chemotherapy | 8 | 4.4 | 3 | 1.5 | 11 | 5.4 | 10 | 5.0 | 0.2043 |
| Supportive care | 11 | 6.1 | 10 | 5.1 | 12 | 5.9 | 11 | 5.4 | 0.9745 |
| Locally advanced disease | | | | | | | | |
| Radiotherapy* | 28 | 53.8 | 49 | 70.0 | 39 | 40.6 | 12 | 12.9 | <0.0001 |
| Chemotherapy | 7 | 13.5 | 3 | 4.3 | 12 | 12.5 | 11 | 11.8 | 0.2720 |
| Chemotherapy+surgery | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.2 | 0.2419 |
| Chemotherapy+radiotherapy* | 11 | 21.2 | 9 | 12.9 | 29 | 30.2 | 55 | 59.1 | <0.0001 |
| Chemotherapy+surgery+radiotherapy | 0 | 0.0 | 3 | 4.3 | 6 | 6.3 | 4 | 4.3 | 0.2247 |
| Supportive care | 6 | 11.5 | 6 | 8.6 | 10 | 10.4 | 9 | 9.7 | 0.9552 |
| Metastatic disease | | | | | | | | |
| Radiotherapy* | 28 | 31.1 | 30 | 24.6 | 17 | 11.5 | 8 | 4.6 | <0.0001 |
| Chemotherapy* | 24 | 26.7 | 32 | 26.2 | 64 | 43.2 | 113 | 65.3 | <0.0001 |
| Chemotherapy+surgery | 0 | 0.0 | 1 | 0.8 | 1 | 0.7 | 2 | 1.2 | 0.0153 |
| Chemotherapy+radiotherapy* | 17 | 18.9 | 4 | 3.3 | 15 | 10.1 | 10 | 5.8 | 0.0003 |
| Surgery | 0 | 0.0 | 0 | 0.0 | 1 | 0.7 | 0 | 0.0 | 0.6754 |
| Chemotherapy+radiotherapy+surgery | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.6 | 0.9999 |
| Supportive care | 21 | 23.3 | 55 | 45.1 | 50 | 33.8 | 39 | 22.5 | 0.0002 |

*Linear trend significant
cisplatin-based chemotherapy with vindesine and/or cyclophosphamide and/or lomustine: 89.3% in 1982–85, and 64.7% in 1986–89. The most common regimen in the last two periods was the combination of cisplatin and vinorelbine: 29.2% in 1990–93, and 32.5% in 1994–97. Use of combined chemotherapy including cisplatin, ifosfamide and/or mitomycin-C began in 1990–93 and increased steeply over the last two periods: 8.4% in 1990–93, and 19.2% in 1994–97. Monotherapy with vinorelbine began in 1986–89, when it constituted 4.4% of the chemotherapy regimens, vs 15.0% in 1994–97.

Simple regressive analysis of relative survival

Overall survival did not change significantly during the study period ($P = 0.861$). Median survival time was 10.3 months during the first period and 10.2 months during the last. For resectable disease, however, improvement of survival over time was on the borderline of statistical significance ($P = 0.066$): MST in this group increased from 21.1 months in 1982–85 to 35.8 months in 1990–93 and decreased slightly thereafter to 33.0 months in 1994–97. No differences from the first study period to the last were observed for locally advanced or metastatic disease ($P = 0.160$), with MST 8.5 and 9.7 months, respectively, in locally advanced disease, and 4.6 and 4.4 months in metastatic disease.

Overall, the 1-, 2- and 5-year survival probabilities were, respectively, 45.9, 29.4 and 15.7%. For patients with resectable disease they were 71.3, 53.9 and 32.6%, and 79.2, 64.2 and 41.1% for those whose tumours were resected. The 1- and 2-year survival probabilities for all patients with locally advanced disease were 38.2 and 15.6%, for those treated by radiotherapy alone, 32.7 and 19.0%, and for those receiving radiotherapy and chemotherapy, 49.3 and 17.6%. These survival probabilities for all patients with metastatic disease were 16.8 and 5.2%, and 45.9, 29.4 and 15.7%. For patients with resectable disease (Table 5): survival rate was higher for those with adenocarcinoma than with squamous-cell carcinoma. In resectable disease (Table 7): survival rate was higher for those with carcinoid tumours than with other histological subtypes.

Multiple regressive analysis of relative survival

The multiple regressive analysis considered age, sex, disease extent, histological subtype, period and treatment in a forward stepwise procedure.

We first included only the pretherapeutic patients’ and disease’s characteristics. Age over 70 years, advanced disease and mixed subtype were less favourable prognostic factors, and the adenocarcinoma and bronchioloalveolar carcinoma histological subtypes more favourable (Table 4).

Then we included, separately for each stage (Tables 5, 6, 7), characteristics of the patients, disease and treatment (because treatment depends strongly on stage). We excluded patients with bilateral disease or undetermined stage. We also excluded treatments administered to fewer than 20 patients, because there was not enough information to allow us to estimate the corresponding coefficient in the model (Table 3).

Age had no prognostic value in the models including treatment variables. Histology was a prognostic factor only in metastatic disease (Table 7): survival rate was higher for those with adenocarcinoma than with squamous-cell carcinoma. In resectable disease, survival was longer among patients undergoing only surgery or surgery and chemotherapy (Table 5). In locally advanced disease, the longest survival was observed with radiotherapy plus chemotherapy (Table 6).

In metastatic disease, patients treated with chemotherapy including new agents or classical agent with platin had a higher

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**Table 4** Multiple regressive survival analysis for pretherapeutic characteristics

| Variables | Hazard ratio | CI          | P    |
|-----------|--------------|-------------|------|
| Age (< 55) | 1            |             |      |
| > 55      |              |             |      |
| Sex       |              |             |      |
| Male      | 1            |             |      |
| Female    | 0.938        | 0.786; 1.120|      |

**Table 5** Multiple regressive survival analysis for pretherapeutic and therapeutic variables in resectable disease

| Variables | Hazard ratio | CI          | P    |
|-----------|--------------|-------------|------|
| Period    |              |             |      |
| 1982–85   | 1            |             |      |
| 1986–89   | 0.978        | 0.831; 1.152|      |
| 1990–93   | 0.897        | 0.764; 1.054|      |
| 1994–97   | 0.911        | 0.777; 1.068|      |
| Histology |              |             |      |
| Squamous-cell | 1          |             |      |
| Adenocarcinoma | 0.844    | 0.733; 0.971|      |
| Bronchioloalveolar | 0.645 | 0.469; 0.886|      |
| Large-cell | 0.972        | 0.807; 1.171|      |
| Mixed     | 1.758        | 1.022; 3.026|      |
| Treatment |              |             |      |
| Surgery alone | 1           |             |      |
| Surgery + radiotherapy | 1.656 | 1.055; 2.598|      |
| Chemo + radiotherapy | 3.761 | 2.336; 6.055|      |
| Surgery + chemotherapy | 0.888 | 0.497; 1.589|      |
| Surgery + radiotherapy | 1.944 | 1.492; 2.533|      |
| Radiotherapy alone | 3.534 | 2.640; 4.730|      |
| Supportive care alone | 5.353 | 3.637; 7.878|      |
| Period    |              |             |      |
| 1982–85   | 1            |             |      |
| 1986–89   | 1.013        | 0.778; 1.319|      |
| 1990–93   | 0.837        | 0.635; 1.104|      |
| 1994–97   | 0.949        | 0.724; 1.245|      |
Table 6  Multiple regressive survival analysis for pretherapeutic and therapeutic variables in locally advanced disease

| Variables          | Hazard ratio | IC   | P   |
|--------------------|--------------|------|-----|
| Sex                |              |      |     |
| Male               | 1            |      |     |
| Female             | 1.538        | 0.972; 2.435 |     |
| Age (years)        |              |      |     |
| ≤ 55               | 1            |      |     |
| 56–70              | 1.155        | 0.845; 1.579 |     |
| > 70               | 1.035        | 0.705; 1.519 |     |
| Histology          |              |      |     |
| Squamous-cell      | 1            |      |     |
| Adenocarcinoma     | 1.147        | 0.802; 1.641 |     |
| Large-cell         | 0.975        | 0.635; 1.498 |     |
| Mixed              | 2.301        | 0.516; 10.267 |     |
| Treatment          |              |      |     |
| Chemo+radiotherapy | 1            |      |     |
| Chemotherapy alone | 2.227        | 1.448; 3.426 |     |
| Radiotherapy alone | 1.457        | 1.034; 2.053 |     |
| Supportive care alone | 3.560 | 2.238; 5.665 |     |
| Period             |              |      |     |
| 1982–85            | 1            |      |     |
| 1986–89            | 0.796        | 0.536; 1.183 |     |
| 1990–93            | 0.974        | 0.678; 1.399 |     |
| 1994–97            | 1.002        | 0.675; 1.467 |     |

Table 7  Multiple regressive survival analysis for pretherapeutic and therapeutic variables in metastatic disease

| Variables          | Hazard ratio | IC   | P   |
|--------------------|--------------|------|-----|
| Sex                |              |      |     |
| Male               | 1            |      |     |
| Female             | 0.895        | 0.696; 1.152 |     |
| Age (years)        |              |      |     |
| ≤ 55               | 1            |      |     |
| 56–70              | 0.908        | 0.725; 1.136 |     |
| > 70               | 0.979        | 0.745; 1.287 |     |
| Histology          |              |      |     |
| Squamous-cell      | 1            |      |     |
| Adenocarcinoma     | 0.751        | 0.607; 0.929 |     |
| Bronchioloalveolar | 0.586        | 0.351; 0.978 |     |
| Large-cell         | 1.023        | 0.788; 1.330 |     |
| Mixed              | 1.361        | 0.553; 3.347 |     |
| Treatment          |              |      |     |
| Chemo+radiotherapy | 1            |      |     |
| Chemotherapy alone | 0.749        | 0.547; 1.026 |     |
| Radiotherapy alone | 0.727        | 0.501; 1.055 |     |
| Supportive care alone | 1.359 | 0.982; 1.881 |     |
| Period             |              |      |     |
| 1982–85            | 1            |      |     |
| 1986–89            | 0.981        | 0.732; 1.315 |     |
| 1990–93            | 1.088        | 0.821; 1.442 |     |
| 1994–97            | 1.272        | 0.949; 1.704 |     |

survival rate than patients treated by classical agent without platin or palliative care only (Table 7).

DISCUSSION

The sex-ratio decreased significantly over time from 10.6/1 in 1982–85 to 6.7/1 in 1994–1997. Analysis of all French registries over this period shows the same trend in sex-ratio for lung cancer: 10.1/1 in 1980 and 6.0/1 in 1995 (Remontet et al., 2003). This trend illustrates the progressive burden of this disease in French women, related to their increasing regular use of tobacco since the end of the Sixties (Hill, 1998), more than two decades after women began smoking regularly in the US (US Public Health Service, 1980). The sex-ratio there is about 2/1 now, and lung cancer is the leading cause of cancer death in women (US Public Health Service, 2001).

The median age at diagnosis among the 1738 patients included in the sample was 63 years, lower than in other European population-based studies, which have found a median age of roughly 70 years (Gregor et al., 2001; Koyi et al., 2002; Mahmud et al., 2003). These series, however, unlike our study, included lung cancer patients (14–26%) not histologically confirmed, the confirmation rates declining with age (Koyi et al., 2002; Mahmud et al., 2003).

The distribution of disease extent also changed significantly during the study period. The percentage of patients with metastatic disease increased, as did the number of metastatic sites and the imaging procedures. This suggests that at least part of the increased frequency of metastatic disease may be due to stage migration, a well-known phenomenon (Feinstein et al., 1985). Cases classified as resectable accounted for 45.2% of the entire sample, and locally advanced stage for only 18.0%. This high percentage of resectable disease probably has two primary causes, the first being the absence of thorax CT scans during the early periods. Second, mediastinoscopy is not routine in France (Depierre et al., 2002), so that patients with stage IIIA disease often undergo surgery.

Disease management changed over the study period, especially for the locally advanced and metastatic stages. Surgery alone remained the primary treatment for resectable disease throughout the period. Combined treatments, such as surgery plus radiotherapy plus chemotherapy or surgery plus chemotherapy, remained relatively infrequent, as seen in a 10-year survey in the US (Fry et al, 1999). The meta-analysis published in 1995 (NSCLC, 1995) did not provide clear evidence that chemotherapy, especially adjuvant chemotherapy, is effective in prolonging survival in these cases. Similarly, only two small randomised studies of neoadjuvant chemotherapy were published during the study period (Rosell et al, 1994). Accordingly, no significant modification in the use of chemotherapy for resectable disease was to be expected.

Use of radiotherapy alone in resectable disease decreased during the study period, while surgery was increasingly used. This observation is consistent with other reports (Janssen-Heijnen and Goepferth, 2003). This trend may be related to advances in operative technique and perioperative care that have prompted greater recourse to surgery (Bolliger and Perruchoud, 1998). Postoperative radiotherapy in resected stage IIIA2 disease is widely used in France as elsewhere (Emami and Perez, 1992) and did not change significantly during the study period.

The PORT meta-analysis confirmed the detrimental effect of postoperative radiotherapy in resected stage I and II disease and found its role in completely resected stage IIIA disease still unclear: an improvement of the local control but no effect on survival (PORT Meta-analysis Trialists Group, 1998).

The use of platinum-based chemotherapy in conjunction with radiotherapy in patients with locally advanced unresectable
NSCLC has become standard in France since the publication by Le Chevalier et al. (1991). In our study, chemotherapy plus radiotherapy in locally advanced disease increased significantly during the study period, from 21.2 to 59.1%. Inversely the use of radiotherapy alone decreased significantly, from 53.8 to 12.9%. Similar trends in the treatment of locally advanced NSCLC have been reported for the US (Fry et al., 1999).

The use of chemotherapy for metastatic disease also increased over time. Practices in our study were consistent with findings in the meta-analysis (NSCLC-CCG, 1995) with cisplatin-based chemotherapy being the most common first-line approach. Many studies reported that cisplatin-based combinations were associated with better response rates and sometimes better survival than monotherapy and these combinations eventually became standard practice (Depierre et al., 1994; Le Chevalier et al., 1994). In this study, 11.7% of the patients treated by chemotherapy received one drug, 39.5% two, 17.8% three, and 31.0% four or more.

We did not see any improvement in overall survival between 1982 and 1997. In the retrospective analysis of patients with extensive NSCLC treated in the clinical trials of the SWOG between 1974 and 1988, an improved survival was observed for those treated with cisplatin-based chemotherapy (Albain et al., 1991), a treatment introduced during the 1980s. The European retrospective analysis of patients with advanced NSCLC enrolled in clinical trials between 1980 and 1991 observed no improvement in survival according to period of diagnosis (Paesmans et al., 1995). A study of 22 years of phase III trials for patients with advanced NSCLC (Breathnach et al., 2001) showed modest progress in survival for these patients: MST increased from 5.2 months in the early period (1973 to 1983) to 5.8 months in the later one (1984 to 1994).

Nevertheless, this improved survival from one clinical trial to another cannot be definitely attributed to improvement of therapies. The increasingly restrictive inclusion criteria may be a factor in the improved outcome of study subjects. These selection biases limit, of course, the generalisability of the results obtained in clinical trials to the real-life population of patients. Comorbidities, often linked to tobacco use, may prevent patients in the general population from receiving the optimal treatment (Janssen-Heijnen et al., 1998). The Will Rogers phenomenon (Feinstein et al., 1985) may also account for at least some of the improved survival observed in consecutive trials.

Leads time bias is another possible explanation for the improvements in survival observed in clinical trials. This bias is the only one of those mentioned here that is also possible in population-based studies, because the general population may also become more aware of lung cancer symptoms over time and consult earlier. Population-based studies are therefore of the utmost importance in assessing treatment efficiency and providing insight into public health policies.

Few population-based analyses of survival in patients with NSCLC have been published. MST of all patients with NSCLC in the SEER-database increased from 9.1 months in 1974–75 to 10 months in 1993–94 and the 3- and 5-year survival rates increased, respectively, by 2 and 4 points (Breathnach et al., 2001). A large hospital-based cancer registry showed no improvement in survival from 1985 through 1995 (Fry et al., 1999).

Elderly patients are excluded from clinical trials frequently and receive optimal treatment less often than younger patients (Earle et al., 2002). Their frequent comorbidities and frailty often preclude administration of the standard treatment (Janssen-Heijnen et al., 1998). But advanced age in itself does not contraindicate aggressive treatment (Deppermann, 2001; Langer et al., 2002). Age was not a prognostic factor in our study when we took into account the specific treatment administered. In various cancers, such as NSCLC (Foucher et al., 1993), studies using relative survival often dismiss age as a significant prognostic factor.

Performance status is probably the best single prognostic factor with stage in NSCLC (Albain et al., 1991). Unfortunately, in this population-based study there were too many missing values. It is not unlikely that more patients with bad PS were histologically diagnosed with lung cancer during the latter end rather than at the beginning of the study period as was demonstrated by UK cancer registries (Cartman et al., 2002). This could at least partially explain the absence of detection of an overall improvement in survival.

We did not observe any protective effect linked to female sex in our study. Several studies report better prognosis for women with NSCLC cancer than for men (Albain et al., 1991; Paesmans et al., 1995; Radzikowska et al., 2002), although not consistently (Keller et al., 2002).

Adenocarcinoma was associated with longer survival in the metastatic stage than squamous-cell carcinoma. The prognostic role of stage and histological type remained controversial in the recently published phase III trials that included hundreds of patients and in this study we observed a trend for those who had surgery and radiotherapy. This combined therapy, however, reflects their advanced pTNM stage: 64.6% of them had post-operative stage IIIA and 11.5% stage IIIB.

In locally advanced disease, the 1-year survival rate was 32.7% for patients treated by radiotherapy alone and 49.3% for those treated with radiotherapy plus chemotherapy. These results are similar to those previously reported in a clinical trial (Le Chevalier et al., 1991). In metastatic disease, the 1-year survival rate was 16.8% for the overall sample, it was 24.1% for the patients who received only chemotherapy, a rate very close to that reported in the chemotherapy arms of clinical trials comparing chemotherapy to the best supportive care (NSCLC-CCG, 1995). Those patients with metastatic disease who were treated with platin-based chemotherapy had the best survival and in this group we observed a trend towards better results with the new agents combined with platin. The recently published phase III trials that included hundreds of patients with advanced NSCLC, did not demonstrate the superiority of any one combination of a platinum salt with a new agent over any other (Kelly et al., 2001; Schiller et al., 2002).

Overall, 16.7% of our patients received only palliative care. This percentage is to be compared to the 14% to 19% in the NCDB series (Fry et al., 1999), 43.2% in the Scottish population-based series (Gregor et al., 2001), and 39.8% in the Irish (Mahmud et al., 2003). The higher percentages in the two latter studies may be partly explained by the inclusion of patients with confirmed lung cancer and probably too frail to undergo diagnostic procedures. However, the survival rates observed in our series are very similar to those reported in recent phase III clinical trials that include highly selected patients.

Several authors argue that SCLC is a more chemoresponsive disease than NSCLC, so that improved survival is more likely to be observed in patients with the former disease (Breathnach et al., 2001; Janssen-Heijnen and Coebergh, 2003). A previous study observed a significant improvement in survival in patients diagnosed with SCLC in the Bas-Rhin between 1981–83 and 1993–94 (Lebistsy et al., 2001). These findings may also reflect the continuing pre-eminence of surgery in curing NSCLC. The benefits of chemotherapy in more advanced disease still appear too small to be translated into
improved overall survival in an entire patient population, some being unable to receive chemotherapy. Thus, the impact of these newer treatments on survival will become apparent when a much greater proportion of patients will be treated with the appropriate treatment, and perhaps the final cohort was too early in the evolution of NSCLC management to outbalance the above factors.

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