

Kazimierz Roszkowski-Śliż

Head of the National Research Institute for Tuberculosis and Lung Diseases

Adjuvant radiotherapy following radical surgery in non-small cell lung cancer

Uzupełniająca radioterapia po doszczętej resekcji w niedrobnokomórkowym raku płuca

This publication was financed by a state-funded grant assigned to the National Research Institute for Tuberculosis and Lung Diseases.

Pneumonol. Alergol. Pol. 2012; 80, 2: 95–98

When considering the study “Evaluation of postoperative radiotherapy in patients with non-small cell lung cancer. A retrospective study” by Chmielewska et al. [1], published in the current issue of “Pneumonologia i Alergologia Polska”, it is hard not to discuss the problem in the context of evidence-based medicine, or rather, no firm evidence-based medicine.

Adjuvant radiotherapy following complete resection of non-small cell lung cancer (NSCLC) has been studied in retrospective studies, randomized studies, and meta-analyses. Patient populations included in these studies were heterogeneous as to histological diagnoses, T and N status, as well as standards of preoperative diagnostics. In many cases, data concerning such important prognostic factors as number of metastatic regional lymph nodes, extracapsular extension, or presence or absence of metastases in subcarinal or subortotal lymph nodes were lacking. Since information concerning radical resection according to the criteria published by the International Association for the Study of Lung Cancer [2] was insufficient or lacking, one may question if radiotherapy applied in these studies was really administered to patients after radical tumour resection.

Key issues in the assessment of surgical procedure radicality include the number of resected

lymph nodes and pathological staging. In 1990 Fernando et al. described a group of 102 patients, in whom intraoperative assessment showed no clinical signs of mediastinal lymphadenopathy. However, routine histopathological assessment in this patient group showed the presence of mediastinal metastases in 24% cases [3].

Keller et al. analysed mediastinal lymph node resections in 373 patients with stage II or IIIA NSCLC, who received adjuvant radiotherapy as part of the Eastern Cooperative Oncology Group (ECOG) study no 3590 [4]. In 187 patients, systematic sampling was used for assessment of N status, and in 186 patients radical mediastinal lymphadenectomy was performed. Higher incidence of mediastinal lymph node metastases was observed in the latter group as compared to the patients assessed by systematic sampling. However, patients who underwent lymphadenectomy survived longer than the other group [4].

In their study, Wu et al. elegantly proved the superiority of mediastinal lymph node resection over systematic sampling for N stage assessment [5]. Prior to lung tumour surgery, random mediastinal systematic sampling of mediastinal lymph nodes was performed in a group of 110 patients with lung cancer. After tumour resection, elective mediastinal lymphadenectomy was performed.

Address for correspondence: Prof. Kazimierz Roszkowski-Śliż MD PhD, National Research Institute for Tuberculosis and Lung Diseases, ul. Płocka 26, 01–138 Warszawa

Manuscript received on: 10.01.2012 r.
Copyright © 2012 Via Medica
ISSN 0867–7077

Systematic sampling underestimated 8.2% cases of lymph node metastases as compared to routine histopathological assessment after surgery. The negative predictive value of systematic sampling was 86.8% for right-sided and 95% for left-sided lymph nodes [5].

Meta-analysis concerning adjuvant radiotherapy in NSCLC was performed by members of the PORT Meta-analysis Trialists Group [6] and included data from seven published randomized studies [7–13] and two unpublished studies, the European Organisation for Research and Treatment of Cancer 08861, and the Lung Cancer Study Group (LCSG) 841.

Analysis included 2128 patients who underwent radical surgery and were randomized to adjuvant radiotherapy or no further treatment. Meta-analysis showed 7% worse two-year survival in patients who received adjuvant radiotherapy (48%) as compared to the no-intervention group (55%).

The mortality rate was higher by 21% in the irradiated patient group, with worse survival in almost all stage I and II patients, and radiotherapy-related toxicity. Radiotherapy had neither positive nor adverse effect on survival in patients with N2 lymph node stage.

The results of the above-mentioned study were widely criticized, not only due to the lack of homogeneous staging methods, especially in assessment of N stage, but also due to the dominant role of one study included in the meta-analysis, in which toxicity-related mortality was particularly high [8]; in the latter study the adjuvant radiotherapy dose was 60 Gy. The study population was also the largest (728 persons) in the meta-analysis, of which 221 patients had stage I, 180 patients stage II, and 327 patients stage III disease.

Results suggesting that adjuvant radiotherapy does not significantly correlate with incidence of local recurrences, and that mortality is not related to disease increases with fraction dose, are interesting but not confirmed by other authors. The report by Machtay et al. entitled “Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma” should be mentioned here, considering their convincing results [14]. The authors compared mortality in patients who received adjuvant radiotherapy using modern planning techniques with mortality due to comorbidities in age- and sex-matched patients who were not irradiated. No statistically significant difference was observed between these two groups.

In 2002 Trodella et al. [12] published results of a randomized phase III study concerning the

effects of adjuvant radiotherapy in patients with stage I NSCLC (T1N0, T2N0). The results of this study contradicted the previously-mentioned meta-analysis. Local recurrence was found in one (2.2%) among all 51 operated patients, who were then irradiated to a total dose of 50.4 Gy, with 1.8 Gy fractions delivered daily for 5 weeks and 3 days. In the control group of 53 patients who underwent only surgical procedures, local recurrences were found in 12 persons (23%). Moreover, there was a tendency for better five-year disease-free survival in irradiated patients (67% vs. 58%; $p = 0.048$).

These results do not prove unequivocally the benefits of adjuvant radiotherapy in terms of survival but confirm that modern radiotherapy administered on a rational basis does not incur unacceptable toxicity in patients operated on for NSCLC. Another positive side of this study is the conclusion that a high incidence of local recurrences (23%) can be a rationale for routine administration of adjuvant radiotherapy, particularly in institutions with worse results of surgical treatment, provided the current criteria of staging and surgical praxis are adhered to [2].

The above-mentioned study was included in another meta-analysis performed in 2005 [16]. The results of the study did not have a significant impact on misanalysis, in which the entire patient population included 2232 patients, and final conclusions remained the same as in 1999.

Lally et al. published a valuable large retrospective analysis of data from the Surveillance, Epidemiology and End Results (SEER) database in 2006 [17]. The authors identified 7465 patients with stage II or III NSCLC, operated between 1988 and 2002. Patients surviving less than 4 months after surgery were excluded from the analysis to eliminate the potential impact of perioperative mortality. Among all the analysed patients, 47% received adjuvant radiotherapy. Multivariate analysis showed no differences in survival between the groups with or without adjuvant treatment. Adjuvant radiotherapy correlated, however, with improved 5-year survival in N2 patients (27% vs. 20%).

The above-cited publication, similarly to both meta-analyses, showed adverse effect of adjuvant radiotherapy on survival in patients with lower disease stage and N0 or N1 lymph nodes. Another study by Lally et al. should be mentioned here. Here, the authors compared cardiological mortality in patients with NSCLC who underwent surgery and adjuvant radiotherapy, in view of the time distribution of the two therapeutic procedures [18]. Adjuvant radiotherapy delivered between 1983–1988 significantly correlated with cardiological

mortality (hazard ratio 1.49), whereas between 1989 and 1993 the analogical risk was 1.08 and statistical significance level was not reached. This observation supports the hypothesis that the introduction of modern radiotherapy techniques contributed to lesser treatment toxicity.

The main reasons for NSCLC treatment failure are distant metastases; therefore, studies on adjuvant chemotherapy after radical surgery have been carried out for many years now. The latest published results suggest that cisplatin-based adjuvant chemotherapy improves 5-year survival in patients with stage II or III disease. Meta-analysis including data concerning treatment of 4584 patients included in five major studies on cisplatin-based adjuvant chemotherapy (Adjuvant Lung Project Italy, Adjuvant Navelbine International Trialist Association, Big Lung Trial, International Adjuvant Lung Cancer Trial, JBR-10) showed improvement of five-year survival by 5.4% [19]. Patients with stage IA disease had adverse prognosis; in stage IB chemotherapy had no impact on survival, whereas adjuvant treatment in stage II or III patients significantly improved their survival [19]. Radiotherapy following adjuvant chemotherapy was recommended but not obligatory in the ANITA study in patients with local lymph node metastases [20]. Comparison of combined treatment (chemoradiotherapy) after surgery with adjuvant chemotherapy alone showed that the addition of radiotherapy was beneficial for overall survival in patients with N2 nodes but had no impact on patients with N1 disease [21].

To sum up, despite all the controversy concerning adjuvant radiotherapy after radical surgery for NSCLC, it is possible that selected patients can benefit from this procedure, mainly in cases with mediastinal lymph node metastases.

Conflict of interests

The author declares no conflict of interests.

References

- Chmielewska E, Jodkiewicz Z, Karwański M. Ocena wyników pooperacyjnej radioterapii u chorych na niedrobnokomórkowego raka płuca. Badanie retrospektywne. *Pneumonol Alergol Pol* 2012; 80: 109–119.
- Rami-Porta R, Wittekind C, Goldstraw P. International Association for the Study of Lung Cancer (IASLC) Staging Committee. Complete resection in lung cancer surgery: proposed definition. *Lung Cancer* 2005; 49: 25–33.
- Fernando HC, Goldstraw P. The accuracy of clinical evaluative intrathoracic staging in lung cancer as assessed by postsurgical pathologic staging. *Cancer* 1990; 65: 2503–2506.
- Keller SM, Adak S, Wagner H et al. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Eastern Cooperative Oncology Group. *Ann Thorac Surg* 2000; 70: 358–365; discussion: 365–356.
- Wu N, Yan S, Lv C et al. Comparison of systematic mediastinal lymph node dissection versus systematic sampling for lung cancer staging and completeness of surgery. *J Surg Res* 2011; 171(2): e169-73. Epub 2011 May 20.
- PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. *Lancet* 1998; 352: 257–263.
- The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med* 1986; 315: 1377–1381.
- Dautzenberg B, Arriagada R, Chammard AB et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancres Bronchiques. *Cancer* 1999; 86: 265–273.
- Debevec M, Bitenc M, Vidmar S et al. Postoperative radiotherapy for radically resected N2 non-small-cell lung cancer (NSCLC): randomised clinical study 1988-1992. *Lung Cancer* 1996; 14: 99–107.
- Lafitte JJ, Ribet ME, Prevost BM et al. Postresection irradiation for T2 NO M0 non-small cell carcinoma: a prospective, randomized study. *Ann Thorac Surg* 1996; 62: 830–834.
- Stephens RJ, Girling DT, Bleeheh NM et al. The role of postoperative radiotherapy in non-small-cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. *Br J Cancer* 1996; 74: 632–639.
- Van Houtte P, Rocmans P, Smets P et al. Postoperative radiation therapy in lung cancer: a controlled trial after resection of curative design. *Int J Radiat Oncol Biol Phys* 1980; 6: 983–986.
- Yom SS, Liao Z, Liu HH et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; 68: 94–102.
- Machtay M, Lee JH, Shrager JB et al. Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma. *J Clin Oncol* 2001; 19: 3912–3917.
- Trodella L, Granone P, Valente S et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. *Radiother Oncol* 2002; 62: 11–19.
- PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database Syst Rev* 2005; 2: CD002142.
- Lally BE, Zelterman D, Colasanto IM et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006; 24: 2998–3006.
- Lally BE, Detterbeck FC, Geiger AM et al. The risk of death from heart disease in patients with nonsmall cell lung cancer who receive postoperative radiotherapy: analysis of the Surveillance, Epidemiology, and End Results database. *Cancer* 2007; 110: 911–917.
- Pignon JP, Tribodet H, Scagliotti GV et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; 26: 3552–3559.
- Douillard JY, Rosell R, De Lena M et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer [Adjuvant Navelbine International Trialist Association (ANITA)]: a randomised controlled trial. *Lancet Oncol* 2006; 7: 719–727.
- Douillard JY, Rosell R, De Lena M et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIa non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008; 72: 695–701.