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Original Article

Prophylactic cranial irradiation in stage IV small cell lung cancer: Selection of patients amongst European IASLC and ESTRO experts

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ABSTRACT

Background: Due to conflicting results between major trials the role of prophylactic cranial irradiation (PCI) in stage IV small cell lung cancer (SCLC) is controversial.

Methods: We obtained a list of 13 European experts from both the European Society for Therapeutic Radiation Oncology (ESTRO) and the International Association for the Study of Lung Cancer (IASLC). The strategies in decision making for PCI in stage IV SCLC were collected. Decision trees were created representing these strategies. Analysis of consensus was performed with the objective consensus methodology.

Results: The factors associated with the recommendation for the use of PCI included the fitness of the patient, young age and good response to chemotherapy. PCI was recommended by the majority of experts for non-elderly fit patients who had at least a partial response (PR) to chemotherapy (for complete remission (CR) 85% of radiation oncologists and 69% of medical oncologists, for PR: 85% of radiation oncologists and 54% of medical oncologists). For patients with stable disease after chemotherapy, PCI was recommended by 6 out of 13 (46%) radiation oncologists and only 3 out of 13 medical oncologists (23%). For

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elderly fit patients with CR, a majority recommended PCI (62%) and no consensus was reached for patients with PR.
Conclusion: European radiation and medical oncologists specializing in lung cancer recommend PCI in selected patients and restrict its use primarily to fit, non-elderly patients who responded to chemotherapy.
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Small cell lung cancer (SCLC) remains a disease with poor prognosis. The gold-standard treatment of stage I–III SCLC consists of concurrent radio-chemotherapy followed by prophylactic cranial irradiation, for patients achieving disease control [1]. Patients with stage IV SCLC receive palliative platinum/etoposide chemotherapy. The Impower 133 trial has shown improvement of progression-free survival (PFS) and overall survival (OS) when adding atezolizumab to carboplatin/etoposide and this regimen may become a new standard of care in suitable patients [2]. The role of prophylactic cranial irradiation (PCI) in stage IV SCLC patients remains controversial [3].

In stage IV SCLC patients who had a response to chemotherapy, PCI has demonstrated not only a significant decrease of symptomatic brain metastases with a hazard ratio of 0.27 (primary endpoint of the study), but also a significant survival benefit with a 1 year survival of 27.1% in the PCI group vs. 13.3% in the control group (secondary endpoint) [4]. PCI in this setting was recently challenged by the results of a Japanese randomized trial showing no survival benefit of PCI in addition to chemotherapy in stage IV SCLC [5]. Important differences between the Japanese and the EORTC studies should be noted. In the EORTC trial no baseline brain imaging was required unless symptomatic, whereas in the Japanese study MRI of the brain was performed both after chemotherapy and 3-monthly during follow-up in the control and the PCI group. The median overall survival for all patients was longer in the Japanese study than in the EORTC trial. The participating Japanese centres, however, included 1 patient per year on average, raising the question whether the results can be generalized to all patients. The majority of patients in the Japanese study developed brain metastases for which radiotherapy was initiated; 46% in the PCI group and 83% in the observation group. As a result of this recent study, the role of PCI is currently deemed controversial and many oncologists consider that follow-up brain MRIs may be an alternative to PCI [6].

In a survey of 93 European thoracic radiotherapy centres, 92 centres (97%) gave PCI routinely [7], however the impact of the Japanese trial is unclear as the survey was developed before the publication of the Japanese trial. Data from the Netherlands Cancer Registry for patients diagnosed with SCLC from 2009 to 2013 showed that 41% of all stage IV patients in the Netherlands received PCI [8]. Age was negatively correlated with the use of PCI in stage IV SCLC in this setting.

Given this situation of conflicting evidence on the role of PCI in routine clinical practice, understanding how clinical experts approach a problem can be of value [9]. In contrast to retrospective series investigating patterns of care, collecting decision trees directly from clinical experts can provide valuable insights into decision making, as such information may often differ from those of clinical trials, databases or health records [10,11].

We therefore performed a decision-making analysis of the role of PCI in the setting of stage IV small-cell lung cancer amongst experts from the European Society for Therapeutic Radiation Oncology (ESTRO) and the International Association for the Study of Lung Cancer (IASLC). This manuscript reports the results for PCI in stage IV SCLC.

Methods

In order to avoid specialty bias [12,13] we collected decision patterns from European radiation oncologists (selected by ESTRO) as well as European medical oncologists (selected by IASLC) from a broad range of countries. Both societies were contacted and asked to provide a list of SCLC clinical experts for this project.

Both ESTRO and IASLC provided a list of 13 experts. Each expert was asked the following question per email: "Under which circumstances would you recommend thoracic radiotherapy and/or PCI for stage IV SCLC? Please describe any disease or patient characteristics relevant for your decision."

The initial responses were collected and converted into decision trees in an iterative process as described previously [14]. The individual decision trees were anonymized and used for analysis to obtain information on areas of consensus or dissent based on the objective consensus methodology [15]. Additionally, criteria that were used by less than 3 experts were omitted from the decision tree analysis. The criteria, which would have precluded PCI, that were removed were: previous irradiation to the area and pre-existing significant neurological impairment. Universal criteria, such as the capacity to give informed consent were also excluded as they would not provide any type of differentiation. Four decision criteria remained relevant, these included fitness of the patient (fit: yes, no), age (elderly: yes, no), thoracic response to chemotherapy (thoracic: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)), and extrathoracic response to chemotherapy (extrathoracic: CR, PR, SD, PD). Specific cut-off values for fitness or age were not defined. Differences in the proportion of experts who recommended PCI amongst radiation and medical oncologists were tested using two-sided chi-squared tests for equality of proportions with continuity correction.

Results

The factors associated with the recommendation for the use of PCI included the general fitness of the patient, age and response to chemotherapy. Response to chemotherapy was sub-classified into intrathoracic and extrathoracic response. Despite this, age was not an absolute contraindication and was not explicitly mentioned as a factor by all participants.

Fig. 1 displays detailed results based on input from all participating experts. PCI was recommended by at least 2/3 of the experts for fit patients, non-elderly and who had at least a partial response to chemotherapy. This was true for both medical and radiation oncologists, with a higher proportion of radiation oncologists recommending PCI (not statistically significant). For patients with stable disease after chemotherapy, PCI was recommended by 6 out of 13 (46%) radiation oncologists and only 3 out of 13 medical oncologists (23%). PCI was not considered an option by any experts for patients with progressive disease after chemotherapy Fig. 2.

For elderly fit patients with CR, a majority recommended PCI (62%) and no consensus was reached for patients with PR.

The tendency to recommend PCI after good response was the same between radiation oncologists and medical oncologists. Even when CR, PR and SD were analysed together, there was no statistically significant difference between medical and radiation oncologists ($p = 0.064$). For non-elderly patients, the majority in both groups recommended PCI, however consensus for PCI was lower amongst the medical oncologists. For elderly patients with CR or PR after chemotherapy, the majority of medical oncologists would

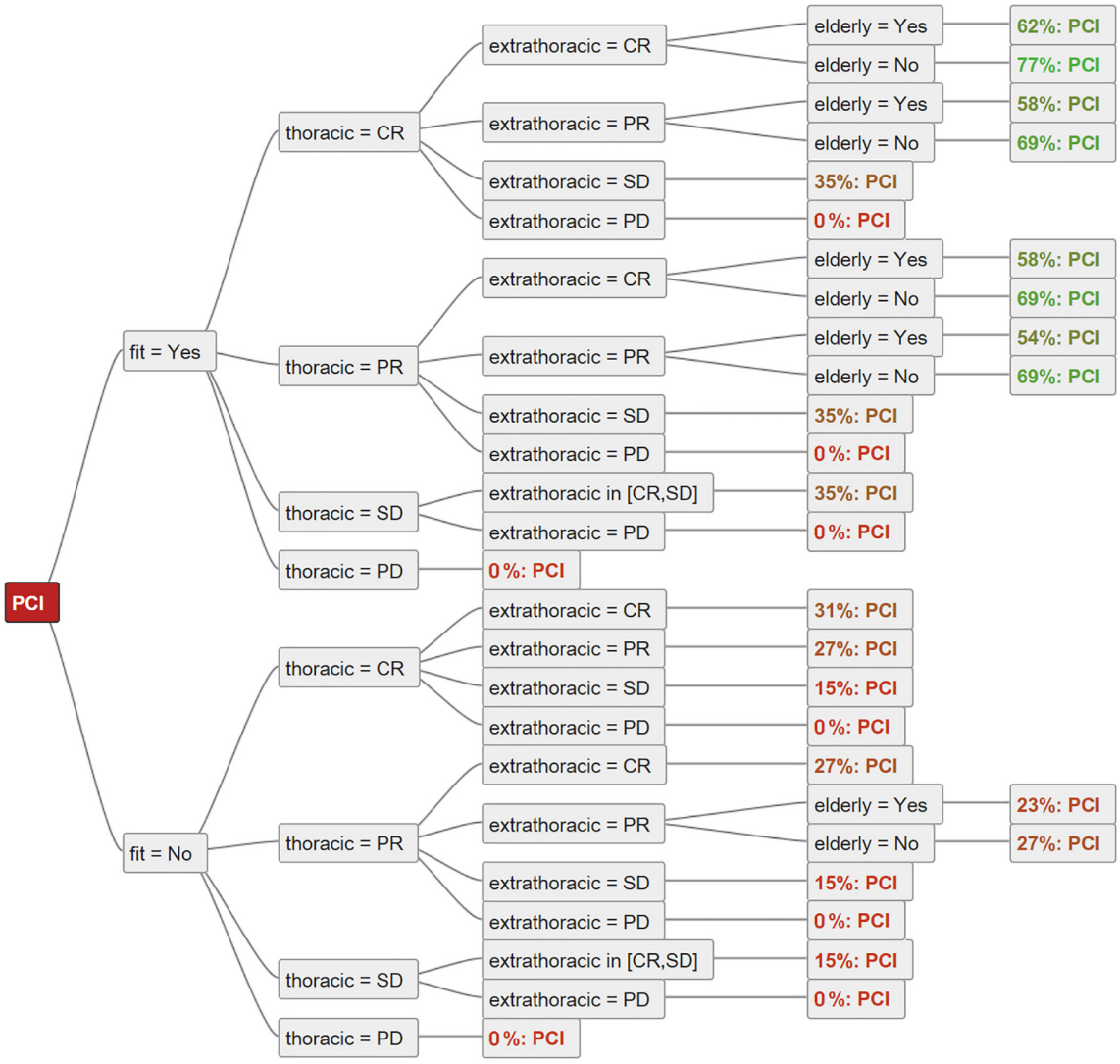

Fig. 1. Decision trees showing the use of PCI in stage IV SCLC amongst medical and radiation oncologists (thoracic and extrathoracic refers to response to chemotherapy in these respective locations, CR-complete response, PR-partial response, SD-stable disease, PD-progressive disease). [CR, SD]-includes complete response, partial remission or stable disease. No consensus represents situations where 50% recommended PCI and 50% recommended no PCI.

Response to chemotherapy	Radiation oncologists	Medical oncologists	p-value
CR	11/13 (85%)	9/13 (69%)	0.64
PR	11/13 (85%)	7/13 (54%)	0.20
SD	6/13 (46%)	3/13 (23%)	0.41
PD	0/13 (0%)	0/13 (0%)	N/A

Fig. 2. Majority recommendations for PCI in young and fit patients based on overall response to chemotherapy comparing radiation and medical oncologists.

not recommend PCI, while amongst radiation oncologists 77% would consider PCI.

Discussion

Following the publication of two international randomized phase III trials, with conflicting results, there is no clear consensus which patients should be offered PCI in stage IV SCLC after chemotherapy. The present patterns-of-decision analysis shows that in fit patients having achieved a response to chemotherapy (CR/PR), the majority of medical and radiation oncology experts would recommend PCI. Nevertheless, medical oncologists were more reluctant to refer patients for PCI than radiation oncologists. Despite the results of the EORTC trial showing a survival benefit in favour of PCI, 15 % of radiation oncologists and approximately 40 % (depending on the remission status) of medical oncologists refrain from the use of PCI. This is likely to be due to fear of neuro-cognitive side-effects in this setting and the option of MRI surveillance.

The three factors relevant to the decision to recommend PCI or not in stage IV SCLC were fitness, age and response to chemotherapy.

Age was simplified into two categories – "elderly" or "not elderly". While a numeric cut-off was mentioned in individual responses, the general consensus was that there is no specific age-dependent cut-off point. While there is evidence that PCI is effective in the elderly population, the absolute benefit is small [16]. In addition to this, elderly patients are at a higher risk of neuro-cognitive side effects after PCI [17].

Response to chemotherapy was a significant factor influencing the recommendation to offer PCI or not. While CR and PR were typically associated with a recommendation to offer PCI, PD was considered a contraindication. This is understandable as the benefit in favour of PCI was demonstrated in patients without progressive disease [4].

The results are based on decision trees populated by experts in the field of SCLC. Although participating experts were selected, rather than by the investigators, by ESTRO and IASLC unaware of the study objective from a range of countries representing different traditions and health-care systems, a slight shift in results with a different selection of experts cannot be excluded. Potentially, the participation of many of the experts within the European PCI trial may cause a bias towards PCI.

While not mentioned as a decision criterion in the decision trees, three participants mentioned that better availability of brain MRIs (easier reimbursement, faster availability) might lead to a reduction in the recommendation to integrate PCI as part of the standard management for stage IV SCLC. However, it should also be considered, that regular brain MRI follow-up every 3 months is associated with significant costs and could be associated with additional patients' anxiety. Furthermore, the benefit of 3-monthly brain MRI in a patient cohort with a high risk for brain metastases and a limited life expectancy remains unclear. However, it should also be noted that the short-term (6 weeks, 3 months) selected health-related quality of life (fatigue and hair loss) was worse in the PCI arm of EORTC trial compared to the control arm [18]. The worsening in global health status was less (8 points on a scale from 0 to 100, not statistically significant).

One of the main motivations to avoid PCI is to spare neurocognitive decline. A recently published randomized trial comparing PCI and observation in NSCLC patients demonstrated grade 1–2 memory impairment and cognitive disturbance at 3 months post-PCI [19]. Quality of life was similar between the arms thereafter, suggesting a positive effect on quality of life through delayed recurrence of brain metastases. The cumulative incidence of symptomatic brain metastases was significantly decreased in the PCI arm (hazard ratio 0.23 [95% CI, 0.09 to 0.56], $p = 0.0012$).

Immune checkpoint inhibitors have made advances in clinical research for SCLC. Preclinical animal studies suggest that checkpoint inhibitors might be able to pass the blood–brain barrier or at least result in a therapeutic response in the brain [20]. Several phase III trials are currently investigating the 'neuroprotective' role of hippocampal avoidance PCI (HA-PCI) and memantine. Whether the role of PCI in the context of HA-PCI (with or without memantine) or immunotherapy will change is currently unclear.

In conclusion, experts from both ESTRO and IASLC, representing European radiation and medical oncologists specializing in lung cancer, recommend PCI in selected patients and restrict its use primarily to fit, non-elderly patients who responded to chemotherapy (CR/PR). Overall, the criteria used by the experts are stricter than the inclusion criteria of the EORTC study. The restricted availability of brain MRI and possible doubt regarding the translation of the Japanese results (different ethnicities and inclusion criteria) may explain why at the time of the analysis, brain MRI surveillance was not suggested by the majority of experts.

A clinical trial comparing PCI to brain MRI surveillance including a thorough evaluation of neurocognitive functions, health-related quality of life and patients reported outcome is warranted.

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