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Prophylactic cranial irradiation in small cell lung cancer:

a systematic review of the literature with meta-analysis.

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Abstract

Purpose: A systematic review of the literature was carried out to determine the role and indications of prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC) .

Methods: To be eligible for the systematic review, full published trials needed to deal with SCLC exclusively and to have randomly assigned patients to receive PCI or not. Trials quality was assessed by two published scores (Chalmers and European Lung Cancer Working Party (ELCWP).

Results: Twelve randomised trials including 1547 patients (798 in the PCI arm and 749 in the control arm) were found to be eligible. Five of them evaluated the role of PCI in SCLC patients who had complete response (CR) after induction chemotherapy. Brain CT scan was done in the work-up in five studies and brain scintigraphy in six. The dose of cranial irradiation ranged from 24 to 40 Gy. Chalmers and ELCWP scores are well correlated ($p < 0.001$), with respective median scores of 32.6 and 38.8 %. This meta-analysis based on the available published data reveals a decrease of brain metastases incidence (hazard ratio (HR): 0.48; 95 % confidence interval (CI): 0.39 – 0.60) for all the studies and an improvement of survival (HR: 0.82; 95 % CI: 0.71 – 0.96) in patients in CR in favour of the PCI arm. Unfortunately, long-term neurotoxicity was not adequately described and its occurrence remains unclear.

Conclusions: PCI decreases brain metastases incidence and improves survival in CR SCLC patients but these effects were obtained in patients who had no systematic neuropsychological and brain imagery assessments. The long-term toxicity has so far not been prospectively evaluated. If PCI can be recommended in patients with SCLC and CR documented by a work-up including brain CT scan, data are lacking to generalise its use to any CR situations.

1. Introduction

Small cell lung carcinoma (SCLC) has a very poor prognosis when untreated. The development of chemotherapy, with or without chest radiotherapy, has allowed to obtain survival improvement and a small percentage of cures. However the majority of the patients relapse and only <25 % of complete responders will be long-term survivors (1).

The central nervous system (CNS) is a frequent site of relapse. About 10 % of the patients initially present with brain metastases. The two-year cumulative risk rises to ≥ 50 % (2) and CNS metastases are found in up to 65 % of patients at autopsy (3). The median survival time after brain metastases diagnosis is 4 to 5 months. Because the blood-brain barrier has been considered to protect the CNS from most cytotoxic agents and as SCLC is very radiosensitive, the role of prophylactic brain irradiation (PCI) has been studied in several trials. The results of the randomised trials show that PCI reduces the frequency of brain metastases although survival is not consistently improved. Some data suggest that the gain in survival is restricted to patients in complete remission (CR). A recently published meta-analysis (4) of PCI for SCLC in patients with CR after chemotherapy has analysed the data of 7 randomised studies (including one abstract and one unpublished study) concerning a total of 987 patients (526 treated with PCI and 461 controls). The relative risk (RR) of death in the treatment group as compared to the control group was 0.84 (95 % confidence interval CI: 0.73 to 0.97; p= 0.01). PCI decreased also the cumulative incidence of brain metastases (RR: 0.46; CI 95 %: 0.38 - 0.57; p < 0.001). Unfortunately the authors have not mentioned the performance of cerebral imagery (CT scan or MRI) in the work-up or the follow-up and have not reviewed the cerebral toxicity of PCI. Some articles have dealt with this question. Johnson (5) reported 20 long-term SCLC survivors with a median follow-up of 6 years (2.4 to 10.6 y). Fifteen SCLC were treated by PCI, 2 by therapeutic cranial irradiation and 3 had no cranial irradiation. Fifteen had neurologic complaints (memory loss, walking or writing difficulties, weakness…), 15 had abnormal brain CT scan (ventricular dilatation, brain atrophy…) and 12 had abnormal mental status examination. Neurologic abnormalities seemed thus to be very common in long-term survivors SCLC and may be more prominent in patients having received high-doses chemotherapy or treated with large brain radiotherapy fractions. Lee (6) reported 3 cases of dementia, confusion and ataxia over 24 patients who received PCI. There was no toxicity in the control group. Toxicity appeared 2.5 years after PCI, the follow-up ranging from 37 to 74 months. In the Chake's study (7), five out of seven patients had progressive dysfunction leading to death in 1 to 26 months after PCI. Foncesca (8) related 14 % leucoencephalopathy in patients with SCLC who received PCI. The mean time of onset of symptoms was 357 days, the median follow-up time being 59 months. Symptoms consisted in intellectual change, memory loss and motor abnormalities. Laukkanen (9) related 60 % memory loss but no dementia two years after PCI. In the Licciardelo study (10), severe neurologic toxicities occurred in two of 15 patients (2.5 and 30 months after PCI). Finally, Van Oosterhout (11) reported no statistical evidence for additional neurotoxicity (follow-up of 2 years) in a series of 51 patients whatever they had received or not PCI. But there was difference in the neuro-psychological examination between patients and matched healthy controls, that might indicate that cognitive impairment is partly disease-related (probably due to emotional distress and deteriorated physical conditions). All these studies being taken in consideration, the problem of cerebral toxicity remains unclear, leading to controversy about the indications of PCI in SCLC.

The purpose of the present article is to assess the role of PCI in SCLC by performing a syste-matic review of the randomised trials published in the literature. A qualitative evaluation of their methodology was performed, including brain imagery work-ups and neuropsychological assessment as well as an aggregation (meta-analysis) of survival and brain relapse results.

2. Materials and Methods

1. Trials selection

To be eligible for the systematic review, trials needed to deal with SCLC exclusively, to have randomly assigned patients to receive prophylactic cranial irradiation or not and to have been published as a full paper in the French or English language literature before January 2000.

Articles were identified by an electronic search (Medline) using the keywords “small cell lung carcinoma” and “prophylactic cranial irradiation” completed by the personal bibliography of one of the authors and by the references reported in the selected studies.

2. Methodological assessment

To assess the trial methodology, nine investigators, including six physicians, one biostatistician, one biologist and one pathologist read each publication, guarantying the critical reading of the selected articles. They were then scored according to two quality scales: the score proposed by Chalmers et al. (12) and the score proposed by the European Lung Cancer Working Party (ELCWP) (13, 14) as described in Appendix A. The participation of many readers was a guarantee for the correct reading of the articles. The Chalmers score evaluates two dimensions of quality: the internal (scientific) and external (generalisability of results) validities, with respectively maximal scores of 63 and 25 points (the total being 88 points). The ELCWP score assesses two quality aspects: the protocol design (as usually reported in the patients and methods section of the publication) and the analysis performance (as reported in the results section) with maximal scores of 70 and 80 points respectively (with an overall maximum of 150 points). Each item was quoted using an ordinal scale (possible values: 2, 1 or 0). When an item was not applicable in a trial, its theoretically attributable points were not taken into account in the total of the concerned category. As the items were defined by data that could objectively be found in the article and did not require a subjective judgement, the score of each item was consensually determined in meetings where at least two thirds of the investigators needed to be present. The final score was expressed in percentage ranging from 0 to 100 %, higher values reflecting a larger application of methodological standards.

3. Statistical methods

The results of a study were considered as “positive” if the p value for the statistical test comparing the survival distributions between arms was < 0.05 in favour of the experimental arm. In the other situations (statistically significant survival benefit for the control arm or non statistically significant difference in survival distributions), it was called “negative”. The same method was used to evaluate the time to relapse in the brain. The correlation between the quality scores, or two other continuous variables, was measured by the Spearman ranks correlation coefficient. Its significance was assessed by testing a null hypothesis of equality to zero of this coefficient. Non-parametric Mann-Whitney (for binary variables) or Kruskal-Wallis (for multiple classes variables) tests were performed to compare quality scores distributions according to the value of the considered discrete variable. For the quantitative aggregation of the survival results, we measured the treatment effect by the hazard ratio (HR) between the survival distribution, according to a method that we have previously reported (15). For each trial, this HR was estimated by a method depending on the results provided in the publications. The most accurate method consisted to retrieve the HR estimate and its confidence interval from the reported results or to calculate them directly using parameters given by the authors: the confidence interval for the HR, the log-rank statistics or its p value or the O-E statistic (difference between numbers of observed and expected events). If not available, we looked for the total number of events and the log-rank statistic or its p value allowing calculation of an approximation of the HR estimate. Finally, if the exploitable data were in the format of graphical representations of the survival distributions, we extracted survivals rates at some specified times in order to reconstruct the HR estimate and its variance with the assumption that the rate of patients censored was constant during the study follow-up. By convention a HR < 1 implied a survival benefit for the experimental arm. The same method was used for time to relapse of the brain.

3. Results

A total of 12 randomised trials (16 - 27) published between 1977 and 1998 were found to be eligible for the present systematic review. Their main characteristics are summarised in table 1. The total number of eligible patients included was 1547; the number of patients by study ranged from 29 to 314 patients (with a median of 81 patients). Seven hundred and ninety eight patients were randomly assigned to the PCI group and 749 patients to the control group. Five studies (894 patients) (16, 17, 19, 23, 27) evaluated the role of PCI in SCLC patients who had a complete response after induction chemotherapy. Five studies (18, 21, 24, 25, 26) assessed the role of PCI administered at induction chemotherapy in patients considered as free of brain metastases. In two studies (20, 22), PCI was given as treatment consolidation at the end of chemotherapy before response evaluation. Seven trials (16, 17, 18, 23, 24, 26, 27) included SCLC patients at all stages of this disease and five studies (19, 20, 21, 22, 25) only limited disease. Brain CT scan was done at the initial staging work-up in five studies (16, 17, 20, 23, 27) and brain scintigraphy in six (18, 21, 22, 24, 25, 26). In one study (19), the staging was only based on clinical examination. The dose of cranial irradiation ranged from 24 to 40 Gy (except in Gregor's study where it was comprised between 8 and 40 Gy). Quality score assessments of the studies are shown in table 2. The overall median quality ELCWP score was 38.8 % (ranging from 24.2 to 70.3 %) with respective protocol design and analyse performance median subscores of 37.7 % (range: 25.0 – 81.0) and 35.2 % (range: 23.1 – 70.9). The linear correlation between protocol design and analyse performance was statistically significant (Rs=0.75; p=0.005). The overall median Chalmers quality score was 32.6 % (range: 11.4 – 75.9 %). There was a significant correlation between both scores (Rs=0.85; p<0.001). There was also a significant difference for ELCWP score according to the year of publication (Rs=0.71; p=0.01), with better quality score for the new recent studies.

The most poorly described items of the ELCWP scale were the work-ups including neuropsychological tests (with a mean score of 22 %), the evaluation criteria (27 %) and the treatment description (33 %) for the internal validity, the prognostic factors for relapse (0 %) or for survival (0 %) and the description of the neurological toxicities (14 %) for the external validity.

Half of the individual studies reported a reduction of brain metastases (16, 18, 19, 25, 26, 27) in the PCI arm but none showed an advantage in term of survival. For the meta-analysis of brain metastases incidence, data were available in 10 trials. The hazard ratio (HR) was provided in 2, it was calculated from the logrank statistic and he number of events in 7 or from the brain metastases incidence curves in one. The meta-analysis revealed a significant decrease in the incidence of brain metastases when all the studies were considered (fig 1) with a hazard ratio (HR) of 0.48 (95 % CI: 0.39 – 0.60) and when only patients in CR were considered (fig 2) with a HR of 0.49 (95 % CI: 0.39 – 0.62). For the meta-analysis of survival, data were available in 11 trials. The hazard ratio was provided in 3, it was calculated from the logrank statistic and the number of events in 6 or from the survival curves in 2. The meta-analysis showed the absence of improvement for survival when all the studies were considered (HR: 0.94; 95 % CI: 0.87 – 1.02) (fig 3) but revealed an improvement in survival when PCI was given to patients in CR (HR: 0.82; 95 % CI: 0.71 – 0.96) (fig 4).

We also performed some subgroups analysis. The decrease in brain metastases incidence was also present in the subgroups of patients with initial PCI, limited disease, any stage disease or who had brain CT scan at initial staging and just before randomisation for PCI (table 3). Results were not significant for survival in patients with initial PCI, limited disease or who had no brain CT scan before randomisation. Statistical significance was marginal in patients with any stage disease or who had brain CT scan for initially staging or just before randomisation for PCI (table 4).

Toxicity was rarely adequately described. There was no data in four studies. In five trials, authors provided a short narrative description mentioning no or minimal toxicity (as alopecia…); Ohonoshi (23) reported one case of seven long-term disease-free survivors who had memory disturbance and gait ataxia in the PCI arm. Two trials reported neuropsychological evaluation in a part of the randomised patients. Gregor (19) performed an assessment of cognitive function in 40 % of the randomised patients and showed no difference between the two arms at two years after PCI but without latter data. Arriagada (16) evaluated 60 % of the patients two years after PCI and showed no difference between the two groups.

4. Discussion

This systematic review, by pooling all randomised studies comparing treatment of SCLC with or without PCI, revealed a positive effect of PCI. As shown by the meta-analysis, PCI reduced brain metastases incidence and improved survival in patients in CR after chemotherapy (especially when brain CT scan was part of the staging work-up). Unfortunately, the performance of brain imagery (CT scan or MRI) and the long-term assessment of neuropsychological toxicities are not well described in the 12 available trials.

To perform a meta-analysis comparing such heterogeneous trials, we have used a methodology that was similar to our prior systematic reviews (14, 15). All trials were assessed by 9 investigators using two quality scores: the Chalmers and the ELCWP scales. The latter scale was adapted to the present topic by introducing some specific changes: in the work-up, brain CT scan or MRI with neuropsychological assessment was needed to have 2 points; in the treatment description, brain irradiation method had to be described; neuropsychological examination results were added in the patients characteristics and the “local control of tumour” item was changed in a “brain metastases incidence” item. The results obtained with the two scales were compared and a significant correlation was observed. There was no quality difference among the publications, allowing quantitative aggregation (meta-analysis) of the results of the individual trials. The only significant finding in the performed comparisons was an improved quality in favour of more recently published trials, which can be explained by a better knowledge of clinical trials methodology standards over the last years.

Our approach does not however prevent all the potential biases. The most important one is probably the publication bias. Our review took into account only fully published studies. We did not look for unpublished trials and abstracts because the methodology used required data available in full publications only. Meta-analysis based on individual data is considered by some authors as the gold standard (28). However in a systematic review of the literature, the studies selection is based on the published trials that provide the data available for everyone. With this method, we nevertheless found the same results for patients in CR as Auperin et al (4) with an individual data meta-analysis. Another potential bias is the language problem: we have restricted our review to articles published in English or French. This selection could favour the positive studies that are most often published in English while the negative ones tend to be more reported in native language (29). The method of extrapolation of HR needs also to be discussed. When HR were not reported by the authors, they were calculated from the data available in the article and, if not possible, they were extrapolated from the survival curves. This approach might have been associated with errors due to imprecision of the reading.

The brain work-up is often poorly documented. Only five studies reported brain CT scan in the initial evaluation and only in two of them, brain CT scan was done just before randomisation for PCI (when patients were in CR after chemotherapy). So, in the majority of the studies, the CR population could contain patients with asymptomatic brain metastases for which the delivered PCI was in fact a consolidation therapy. To be sure that there are no brain involvement, brain CT scan should have been done just before PCI. In addition, the CR status depends on the type of work-up performed and on the presence of lesions due to chest irradiation, explaining probably why some groups report small rates of complete response. Moreover, the recent development of MRI that could reveal smaller asymptomatic brain metastases will require an update of these trials in the next few years. Indeed, in contrast to prior literature which showed a prevalence of brain metastases at presentation of 10%, Hochstenbag et al found a prevalence of 24 %. This difference can been explained by the fact that the prevalence of 10 % is based on clinical signs and confirmation by brain imaging and, that in the Hochstenbag's study, MRI diagnosed 15 % brain metastases in neurologically asymptomatic patients (30).

The neuropsychological toxicity of PCI was only described in retrospective studies performed with a small number of patients. In our review, two randomised trials reported neuropsychological assessments that was performed only in a part of the patients and during the first years following PCI. They provided no data about long-term toxicity. It should be noted that other factors than radiotherapy toxicity can also contribute to neurological complications. Indeed old age, alcohol, anticancer drugs (vincristine, etoposide,…), paraneoplastic encephalomyelitis and tobacco long-term use or can produce demential syndromes. Concomitant administration of some types of chemotherapy is considered to contribute to brain radiotherapy toxicity. The fractionation and the total dose of radiotherapy delivered to the brain can also influence the toxicity. Neurological toxicity may be reduced by using 2 Gy fractions (20 to 40 Gy) and by giving PCI after chemotherapy. All these factors were not analysed in our systematic review because of a total lack of data in the report of the results of the individual randomised trials.

In conclusion, the present systematic review indicates that PCI decreases brain metastases incidence and that PCI improves survival in SCLC patients in CR after chemotherapy. These effects were obtained in patients who had no systematic neuropsychological brain imagery assessments. The long-term toxicity has so far not been prospectively evaluated. If PCI can be recommended in patients with SCLC and CR documented by a work-up including brain CT scan, data are lacking to generalise its use to any CR situations as some would like (31). Particularly the potential benefits of PCI have to be carefully balanced with the possible long-term effects, in patients who are managed with more modern imagery techniques like MRI. New trials, adapted to these new developments, are necessary.

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Table 1: Trials characteristics

Authors	Dates	Stage	Cerebral work-up	PCI (Gray)	Timing of PCI administration	N patients
Jackson (18)	1977	1	2	30	1	29
Beiler (24)	1979	1	2	24	1	54
Hansen (22)	1980	2	2	40	3	109
Maurer (26)	1980	1	2	30	1	153
Eagan (20)	1981	2	1	36	3	30
Aisner (27)	1982	1	1	30	2	29
Seydel (21)	1985	2	2	30	1	217
Niiranen (25)	1989	2	2	40	1	51
Ohonoshi (23)	1993	1	1	40	2	46
Arriagada (16)	1995	1	1	24	2	294
Gregor (19)	1997	2	3	8 - 40	2	314
Laplanche (17)	1998	1	1	24	2	211

Stage: 1: all

2: limited disease

Cerebral work-up: 1: brain CT scan

2: brain scintigraphy

3: clinical

Timing: 1: at initiation of chemotherapy

2: CR consolidation

3: consolidation only

Table 2: Quality Scores assessment

Authors	ELCWP Score			Chalmers Score			SMA	BMI MA
	PD (%)	AP (%)	Total (%)	IV (%)	EV (%)	Total (%)		
Arriagada (16)	81.0	70.9	70.3	84.2	54.5	75.9	Yes	Yes
Laplanche (17)	59.3	58.1	58.7	50.0	40.9	47.6	Yes	Yes
Jackson (18)	30.3	35.7	33.2	21.0	27.2	22.8	Yes	Yes
Gregor (19)	69.0	49.6	58.7	59.5	27.2	51.1	Yes	Yes
Eagan (20)	33.0	40.4	36.9	28.5	20.4	24.7	Yes	No data
Seydel (21)	25.0	28.0	26.6	14.3	13.6	14.1	Yes	Yes
Hansen (22)	52.3	31.6	41.3	47.6	40.9	45.9	Yes	No data
Ohonoshi (23)	38.0	43.1	40.7	42.8	54.5	47	Yes	Yes
Beiler (24)	25.4	23.1	24.2	33.3	13.6	28.2	Yes	Yes
Niiranen (25)	48.9	34.7	41.3	40.4	27.3	37	Yes	Yes
Maurer (26)	36.9	31.1	33.8	23.8	13.6	22.3	Yes	Yes
Aisner (27)	37.4	28.7	32.8	10.5	13.6	11.4	No data	Yes

Mean	44.7	39.6	41.5	38.0	28.9	35.7
Median	37.7	35.2	38.8	36.9	27.2	32.6

PD : protocol designed

AP : analysis performance

ELCWP : European Lung Cancer Working Party

IV : internal validity

EV : external validity

SMA : survival meta-analysis (studies evaluables)

BMI : brain metastasis incidence meta-analysis (studies evaluables)

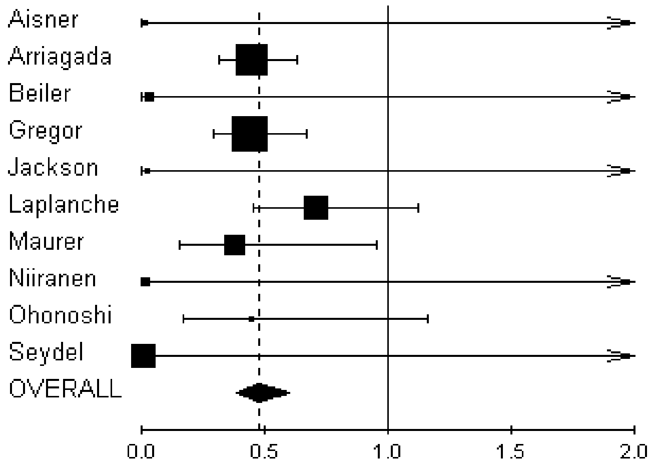
Table 3: Subgroup meta-analysis: role of PCI on brain metastases incidence (10 studies evaluable)

	n studies	HR
Initial PCI	5	0.29 (0.12 – 0.71)
Limited disease	3	0.43 (0.28 – 0.64)
All stages diseases	7	0.50 (0.39 – 0.65)
Brain CT scan for staging	4	0.52 (0.40 – 0.68)
Brain CT scan before randomisation	2	0.44 (0.32 – 0.62)
No CT scan before randomisation	2	0.51 (0.38 – 0.63)

Table 4: Subgroup meta-analysis: role of PCI on survival (11 studies evaluable)

	n studies	HR
Initial PCI	5	1.00 (0.91 – 1.09)
Limited disease	5	0.98 (0.90 – 1.07)
All stages diseases	6	0.84 (0.72 – 0.98)
Brain CT scan for staging	4	0.82 (0.68 – 0.98)
Brain CT scan before randomisation	2	0.78 (0.62 – 0.98)
No CT scan before randomisation	2	0.96 (0.88 – 1.04)

Fig 1: Results of the meta-analysis of the studies evaluating the role of PCI on brain metastases incidence : HR : 0.48 (95% CI : 0.39-0.60)



NB: the centre of the lozenge gives the combined HR of the meta-analysis and its extremities the 95% confidence interval.

Fig 2: Results of the meta-analysis of the studies evaluating the role of PCI on

brain metasta

ses incidence when patients are in complete response : HR : 0.49 (95% CI :

0.39-0.62)

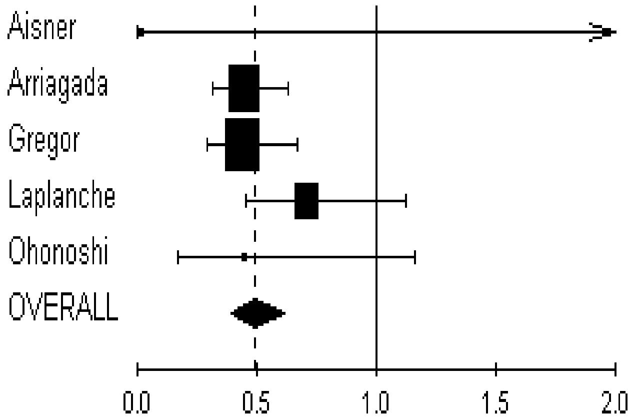


Fig 3: Results of the meta-analysis of the studies evaluating the role of PCI on survival : HR : 0.94 (95 % CI : 0.87-1.02)

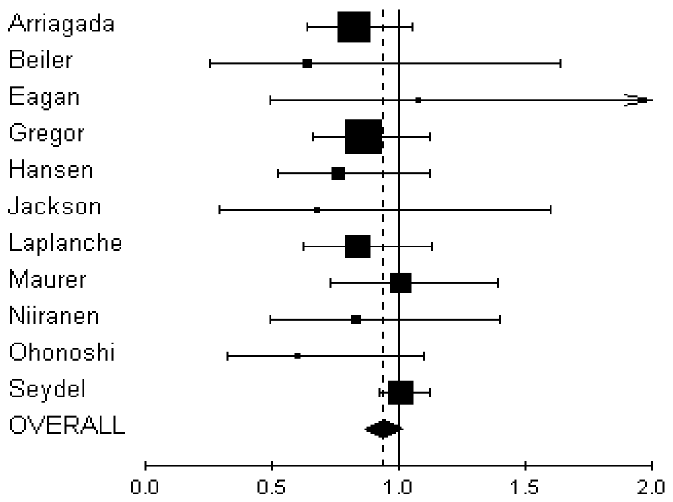
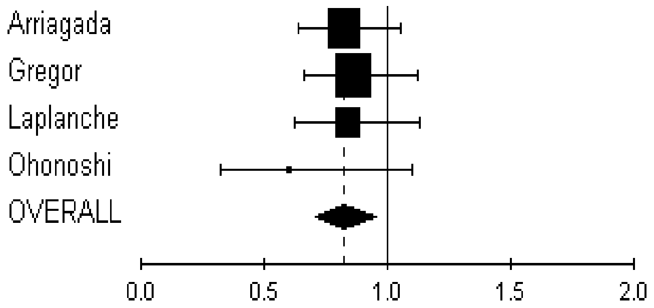


Fig 4: Results of the meta-analysis of the studies evaluating the role of PCI on survival when patients are in CR : HR : 0.82 (95% CI : 0.71-0.96)



Appendix A: ELCWP Quality Score

The attributed value per item is 2 points if it is clearly defined in the article, 1 point if its description is uncomplete or unclear and 0 point if it is not defined or inadequate.

A. Protocol Design

1. definition of the number of participating centres
2. selection criteria :
   - PS
   - age
   - disease stage
   - other anticancer treatment
   - comorbidity
   - histology
3. randomisation method
4. treatment description
   - PCI : total dose, fractions, duration, fields, kind of energy
   - dose adaptation plan
5. work-up :
   - initial : brain CT scan or MRI and/or neuropsychological assessment
   - at response assessment (idem)
   - during follow-up after therapy (idem)
   - brain CT scan or MRI : systematically or not

6. evaluation criteria
    - brain metastases free duration
    - survival
    - toxicity
    - neuropsychological assessment
7. statistical methods
    - primary and secondary objectives definition
    - statistical methods and tests used
    - a priori estimate of sample size

B. Analysis Performance

1. analysis timing
    - dates of first and last patient registration
    - type of analysis (definitive or planned interim)
2. patients characteristics
    - ineligibility rate (per arm)
    - causes for ineligibility
    - eligible patients characteristics :
        - age
        - performance status
        - sex
        - disease extent or stage
        - neuropsychological assessment
        - time to PCI
        - chemotherapy description
        - arms balance according to stratification
3. survival
    - rates
    - crude numbers of deaths

- confidence intervals on rates
- statistical tests results
- intent to treat analysis

4. brain metastases incidence
   - rates
   - crude numbers of deaths
   - confidence intervals on rates
   - statistical tests results
   - intent to treat analysis
5. neurologic toxicity
   - descriptions per arm
   - unassessable rate
   - statistical tests results
   - confidence intervals on rates
6. prognosis factor for survival
   - univariate analysis
   - multivariate analysis
7. prognosis factor for brain metastases
   - univariate analysis
   - multivariate analysis

8. discussion

- authors conclusions in accordance with results
- for negative trials : a posteriori estimate of study power

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Reviewers' Reports

Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis

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The publication by Dr Anne-Pascale Meert et al. dealt with an important question regarding small cell lung cancer (SCLC) therapy: Is there a case for prophylactic cranial irradiation (PCI) in patients responding to chemotherapy? The author performed a meta-analysis based on published data and confirmed that PCI reduces the risk of relapse to the brain (with an hazard ratio (HR) of .48 [95 % confidence interval: .39 - .60]) and also reduces the risk of death, although to a lesser extent (HR: .82; [.71 - .96]). Dr Meert's report emphasised the fact that no clear conclusion can be stated regarding the putative neurotoxicity of PCI insofar as most of the aggregated publications did not report this outcome correctly. In fact, only two out of twelve publications reported on neurospychological consequences of PCI. Even with these two studies, the late effects could have been under-estimated. This interesting meta-analysis merits to be put into perspective with recently published literature on this subject.

In a way, the present meta-analysis confirms Dr Anne Aupérin's meta-analysis based on individual data in the same field (1). The above-mentioned HRs are closely consistent with those reported with individual and updated data (HR of risk of death: .84 [.73 - .97] and HR of risk of relapse to the brain: .46 [.38 - .57]). Although the results from the two meta-analyses regarding the main end-points were similar, they differed on a methodological point of view; Dr Meert's meta-analysis included more patients than Dr Aupérin's did (1547 versus 987, corresponding to a 1.56 ratio for analysed patients). The reason for this difference might be due to the restrictive inclusion criteria taken into account in the first published meta-analysis: only seven studies randomising patients pending on a complete remission status were aggregated.

One may hypothesise that, due to the nature of this meta-analysis based on published data, a possible bias was introduced. As stated by the author, the procedure did not allow the disclosure of unpublished trials. A direct comparison of meta-analysis on medical literature and meta-analysis on individual patient

data has been performed in the setting of cisplatin-based chemotherapy in ovarian cancer (2). This study suggested possible differences in estimated treatment effect due to patient exclusions and shorter length of follow-up in the former technique. On the other hand, the consistency of findings by Dr Meert's and Dr Aupérin's meta-analyses is an interesting example of congruent appraisals of a sole question using two different methods.
As a first step in their meta-analysis, Dr Meert et al. performed a comprehensive analysis of publication quality. Overall quality of the publications increased from the earliest to the latest. Therefore, it would have been of interest to statistically test the heterogeneity, even if the HRs within the different studies looked concordant from a graphical point of view.

Neurotoxicty analysis in PCI programmes is a complex issue. The first limitation of its appraisal comes from the fact that late effects are difficult to assess owing to the low rate of long survivors. The second difficulty is related to the high frequency of neurological and psychological abnormalities at the time of SCLC diagnosis. Among the different aetiologies, one can note that paraneoplastic syndromes due to anti-Hu or Anti-Yo antibodies are probably under-diagnosed. The occurrence of anti-Hu related symptoms such as encephalomyeloneuritis remains unclear. Whether or not SCLC patients presenting with serum anti-Hu antibodies develop neurological symptoms depends on the antibody response, comprising predominantly of IgG subclasses able to fix to the complement (3). These paraneoplastic symptoms are known to persist (or eventually appear) once a complete remission has been achieved (4). This could lead to confusing analyses of treatment-related neurotoxicity. Third, most of the globally accepted chemotherapies in SCLC could induce neurological or psychological abnormalities that can in turn enhance the PCI toxicity.

In conclusion, Dr Meert's meta-analysis is an additional clue in favour of PCI reducing both risk of death and risk of relapse to the brain. However, important issues remain unanswered. Because toxicity is influenced by both total dose and fractionation of PCI, one can suggest that studies aiming to determine the optimal dose such as the one chaired by Dr Cécile Le Péchoux in the Gustave Roussy Institute (France, lepechou@igr.fr) are urged.

Pr Jean-Louis Pujol

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My evaluation of Dr Meert's paper would be as follows:
1. The conclusions are supported by the data
2. The method is well described and the results are in agreement with previous meta-analysis in the same field.
3. The manuscript adheres to the relevant standards for reporting
4. This is a well written paper.

Level of Interest:
A paper of considerable general medical or scientific interest.

Advice on Publication:
Accept after revision minor revision (see the paragraph regarding the need to statistically test the heterogeneity between studies).

Competing Interests:
None declared

Richard Stephens

It is not at all clear to me what this paper adds to the literature. In areas where there is some clinical uncertainty the logical progression is to first do a systematic review of the literature and if that looks interesting to do a individual patient data meta-analysis (IPD MA). However with regards to prophylactic cranial irradiation in small cell lung cancer the IPD MA has already been published (Auperin et al, NEJM 1999, 341, 476-484).

The current paper does not add any new publications. It includes 7 older trials (from the 1970s and 80s) which were excluded by the IPD MA as randomisation to PCI or No PCI was performed before response was assessed, but leaves out 3 trials (2 published only as abstracts, and 1 unpublished trial) which were included in the IPD MA. Nevertheless the results of this systematic review are remarkably similar to the IPD MA results.

It is certainly true that despite all the trials we still do not have clear evidence of the long-term neurological effect of PCI. Studies such as Cull et al (EJC 1994, 30A, 1067-1074) have found a significant degree of cognitive dysfunction in long-term SCLC survivors who have received PCI, but it is not known how much of this is due to PCI and how much to SCLC itself. However with the benefits in survival and reduction of brain metastases highlighted by the IPD MA and this paper, it is difficult to see how we could go back and run trials of PCI vs No PCI with the specific aim of assessing long term problems. Apart from the ethical problem of such a trial, one would need a very large trial in order to get sufficient long-term survivors in each arm.

The role of the ELCWP and Chalmers Quality Scores in this paper is also not clear. Firstly these measures assess the quality of the report not the trial, and the former may be compromised by the limitations of length in some journals. Secondly if scores are calculated should they then not be used in some way to weight the importance of the trial, or cut-offs set to exclude trials?

Although there seems some logic in doing a cerebral work-up in patients before giving PCI, how exhaustive should this be? There is no evidence that the trial (Gregor et al EJC 1997, 33, 1752-1758) which used only clinical assessment gave different results from the others which used brain CT or scintigraphy.

I would like to warn against the use of outcomes such as ‘appearance of brain metastases’ in isolation. It is much better to present outcomes such as brain metastases-free survival, as, for instance, patients receiving a very toxic regimen that causes many early deaths may as a consequence appear to have a very low rate of local recurrence. This may explain the greater reduction of brain metastases but lack of survival difference in the subgroup analyses of trials that used ‘initial PCI’.

As the subgroup analyses presented in Figures 2 and 4, and Tables 2 and 4 are merely subdivisions of Figures 1 and 3 it might be clearer simply to present 3 forest plots of survival and brain metastases subdivided by response group, stage, and cerebral work-up.

Level of interest:
Sound Paper of limited interest

Advice on publication
I really don't know – it's not scientifically unsound – just doesn't add anything

Quality of English:
Acceptable

Competing interests:
None, although I was an author of the MA paper (Auperin et al)