



Omission of Prophylactic Cranial Irradiation in the Management of Limited-Stage Small-Cell Lung Cancer: Is that Ready for Prime-Time? An International Survey

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Abstract

Background and Purpose: Prophylactic Cranial Irradiation (PCI) is considered as standard of care for patients with Limited Stage Small-Cell Lung Cancer (LS-SCLC). Several clinical studies demonstrated a narrow survival benefit for PCI. However, all of them were completed before the wide introduction of Magnetic Resonance Imaging (MRI) for diagnosis and follow up of brain metastases. Therefore, a requirement for PCI is uncertain when brain involvement can be excluded by MRI-scan. We conducted an international survey attempting to gauge the attitude of oncology professionals to possible replacement of PCI by close MRI-based surveillance in the management of LS-SCLC.

Materials and Methods: A questionnaire was designed to survey the attitudes of medical and radiation oncologists toward PCI in LS-SCLC. An invitation was sent to 638 medical and radiation oncologists by e-mail obtained from professional society directories. The e-mail contained a link to an online platform where the survey could be accessed.

Result: Responses were received from 61 oncologists employed by 47 centers, located in 15 countries. Omission of PCI in favor of MRI-based surveillance was supported by 36.1% of respondents. This support was significantly higher among medical as opposed to radiation oncologists ($p=0.022$). The majority of responders considered stereotactic radiosurgery as the preferred salvage therapy for brain metastases in both PCI-naïve and PCI-exposed patients.

Conclusion: A substantial proportion of cancer specialists can support omission of PCI in favor of regular MRI-based follow up for patients with LS-SCLC. A randomized controlled trial is highly warranted to resolve the debate.

Keywords: Small-cell lung cancer; Prophylactic cranial irradiation; Survey

Introduction

Small-Cell Lung Cancer (SCLC) is overall a highly aggressive poor prognosis tumor with a 5-year survival not exceeding 10% [1]. However, in Limited-Stage SCLC (LS-SCLC) when tumor is confined to a sole hemi-thorax and is encompassable within a single radiation volume, 5-year survival can increase to 25% by aggressive treatment with concurrent chemoradiation [2,3]. Yet, even in LS-SCLC there is a high propensity to develop distant metastases within 2 years after diagnosis [4]. Brain is considered a common site of distant metastases in patients with SCLC [5].

Current management of LS-SCLC comprises of chemotherapy given concurrently with thoracic radiotherapy, followed by Prophylactic Cranial Irradiation (PCI) for patients responding to initial therapy [6]. This guideline has been based on several clinical trials and meta-analyses, which demonstrated decreased incidence of intracranial metastases by 17% to 30%, and increased 3-year survival by 8% to 12% with the addition of PCI [7-10]. However, these studies were conducted before the era of Magnetic Resonance Imaging (MRI). Furthermore, brain imaging for asymptomatic patients was not even mandatory in many of those trials. MRI has a greater sensitivity for detection

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Table 1: Characteristics of 61 cancer professionals participating in the survey.

Characteristic		
Country of practice	Number of cancer centers/respondents	Number of lung cancer patients treated per respondent annually (average/range)
Austria	2/4	450/100-800
Belgium	1/1	200
Bulgaria	1/1	50
Czech Republic	2/4	175/150-200
France	5/7	600/300-1300
Germany	3/3	800/300-1100
Greece	7/9	111/20-300
Hungary	2/2	1110/720-1500
Israel	7/9	318/40-600
Italy	3/3	300/200-400
Netherlands	1/1	440
Poland	1/1	400
Spain	3/3	183/50-250
Turkey	3/3	300/200-500
USA	5/9	440/250-1000
Total	47/61	392/40-1500
Type of practice	Number of cancer centers (absolute/per cent)	
Academic	33/70.2	
Public	9/19.2	
Private	5/10.6	
Profession	Number of respondents (absolute/per cent)	
Medical oncology	48/78.7	
Radiation oncology	13/21.3	

of asymptomatic brain metastases as compared with Computed Tomography (CT) [11]. Thus, it could be postulated that PCI was not in fact prophylactic when used in studies, but rather was a therapeutic intervention to treat asymptomatic brain metastases undetected by CT-scan, which possibly translated to a survival advantage for PCI [10]. Based on this assumption, patients in the study arm who in fact had no brain disease, were probably over treated, and were at risk to experience some degree of neurologic toxicity and decline of cognitive function [12-15].

A proposed alternative treatment algorithm is replacement of PCI by periodic MRI-based brain monitoring and administering brain radiotherapy only on the appearance of brain metastasis. A recently published survey of 309 practicing United States (US) based radiation oncologists revealed reluctance to abandon PCI in favor of close MRI-based surveillance [16], with 98% of respondents agreeing with the guidelines of National Cancer Comprehensive Network (NCCN) on management of LS-SCLC, including the use of PCI [6]. However, this survey was completed before publication of randomized data, which showed the absence of a PCI survival advantage when brain MRI was used to follow up patients with Extensive Disease SCLC (ED-SCLC) [17]. In addition, medical oncologists, who may not share the same views as the radiation oncologists on this issue, were not included in this survey. Furthermore, the possibility of using Stereotactic Radiosurgery (SRS) for salvage management of brain metastases in patients with SCLC was not addressed. So far, there has not at yet been a randomized controlled trial to resolve the question of the role

of PCI in the management of LS-SCLC.

We conducted an international survey of medical and radiation oncologists in order to help in providing a basis for a randomized controlled trial to compare PCI and MRI-surveillance in the management of LS-SCLC.

Materials and Methods

The survey was designed to include both medical and radiation oncologists and was approved by the Soroka University Medical Center Institutional Review Board. The survey questionnaire contained 39 questions, which covered demographic information including country of practice and medical center, as well as treatment and follow up practice of the study respondent for patients with LS-SCLC (see appendix).

We invited for participation medical and radiation oncologists, affiliated with various medical centers and practices, whose emails were, listed in the membership directories of the US, European and Israeli professional societies. An invitation message contained a link to the survey-monkey platform upon which the questionnaire was placed [18], and also included information about the study, instructions for completion, and contact data. In addition, respondents were also asked whether their practice pattern represented a therapeutic policy of the institutions they were employed by.

Responses were summarized for the entire pool and by professional groups. The Chi-square test was used to evaluate the

differences in responses between medical oncologist and radiation oncologists for the categorical variables [19].

An initial invitation to participate in the survey was sent on December 07th, 2018 to 638 radiation and medical oncologists at cancer centers in Europe, the US and Israel. Invitees who asked not to be contacted again were removed from data base. The final date for receiving completed questionnaires was October 31st, 2019.

Results

Completed questionnaires were received from 61 respondents, practicing in 47 cancer centers located in 15 countries. Characteristics of respondents are presented in Table 1. At the time of completing of questionnaire, over 70% of respondents were employed by academic bodies. The majority were medical oncologists (78.7%). All respondents confirmed that their practice patterns in the management of LS-SCLC were consistent with the guidelines adopted by their employing cancer centers.

The approach of respondents to initial diagnosis, management of non-metastatic brain, and follow up of patients with LS-SCLC is summarized in Table 2. Positron emission tomography (PET-CT) was favored over conventional CT for initial systemic evaluation by medical (79.2%) and radiation (100%) oncologists ($p=0.44$). Likewise,

MRI was preferred over CT by both medical (87.5%) and radiation (100%) oncologists to rule out brain metastases ($p=0.68$).

Brain MRI was considered as a part of initial staging of LS-SCLC by 90.2% of respondents. The majority (63.9%) considered PCI mandatory after completion of chemoradiotherapy. The percentage of medical oncologists favoring PCI was significantly lower than the percentage of radiation oncologists favoring PCI (56.2% vs. 92.3%, $p=0.022$). In terms of dose of PCI, a low radiation dose regimen of 20 Gy to 25 Gy in 10 fractions was preferred by 60.6% of all respondents. Regular MRI-follow up after PCI was recommended by 47.5% of respondents. However, 19.7% of participants considered post-PCI brain imaging unnecessary for asymptomatic patients.

For treatment of diagnosed brain metastasis, SRS was overwhelmingly supported by both medical and radiation oncologists for treatment of 1 to 3 brain metastases (87.5% and 100% respectively, $p=0.68$) in patients with LS-SCLC unexposed to PCI. There was substantial support in both specialties for administering SRS to treat more than 3 brain metastases (66.7% vs. 61.5%, $p=0.78$). SRS for managing of 1 to 3 brain metastases after PCI was preferred by 93.8% of medical and 100% of radiation oncologists ($p=0.96$). Only 27.1% of medical oncologists supported using SRS in patients with more than 3 brain metastases, as compared to 61.5% of radiation oncologists

Table 2: Attitude of 61 responders to brain management in patients with LS-NSCLC.

Variable	Number of respondents (absolute/per cent)			
	Total (61)	By profession		
		Radiation oncologists (13)	Medical oncologists (48)	p-value (Chi-square test)
Imaging preferred for initial staging				
PET/CT	51/83.6	13/100	38/79.2	0.21
CT	10/16.4	0/0	10/20.8	
Imaging preferred for detecting brain metastases				
MRI	55/90.2	13/100	42/87.5	0.38
CT	6/9.8	0/0	6/12.5	
Management of intact brain				
PCI	39/63.9	12/92.3	27/56.2	0.022
MRI-based follow up	22/36.1	1/7.7	21/43.8	
Preferred schedule of PCI				
25 Gy in 10 fractions	26/42.6	9/69.2	17/35.4	0.07
20 Gy in 10 fractions	11/18	0/0	11/22.9	0.39
30 Gy in 10 fractions	10/16.4	2/15.4	8/16.7	0.94
30 Gy in 15 fractions	6/9.9	1/7.7	5/10.4	0.78
No preference	8/13.1	1/7.7	7/14.6	0.95
Follow up imaging after PCI				
MRI	29/47.5	9/69.2	20/41.7	0.31
CT	20/32.8	3/23.1	17/35.4	0.49
No if asymptomatic	12/19.7	1/7.7	11/22.9	0.39
SRS for management of brain metastases Pts unexposed to PCI				
1-3 metastases	55/90.2	13/100	42/87.5	0.38
>3 metastases	40/65.6	8/61.5	32/66.7	0.39
Pts after PCI				
1-3 metastases	58/95.1	13/100	45/93.8	0.48
>3 metastases	40/66	8/61.5	13/27.1	0.028

Pts: Patients; CT: Computerized Tomography; PET: Positron-Emission Tomography; MRI: Magnetic Resonance Imaging; SRS: Stereotactic Radiosurgery

Table 3: Support for prophylactic cranial irradiation in countries participating in survey.

Country of practice	Number of PCI -supporters (absolute/per cent)
Austria	3/75
Belgium	0/0
Bulgaria	1/100
Czech Republic	1/50
France	4/57.1
Germany	3/100
Greece	7/77.8
Hungary	2/100
Israel	4/44.4
Italy	1/33.3
Netherlands	1/100
Poland	1/100
Spain	3/100
Switzerland	3/100
Turkey	3/100
USA	2/22.2

*PCI: Prophylactic Cranial Irradiation

(p=0.028).

Discussion

We conducted an international survey of medical and radiation oncologists in order to compare their attitude to the possible replacement of PCI by MRI-based surveillance in the management of LS-SCLC patients responsive to initial chemoradiotherapy. The majority of respondents practiced in academic institutions. All respondents made a clear statement that their practice patterns were consistent with the guidelines for management of LS-SCLC adopted by the cancer centers they worked for. A significant proportion (36.1%) of the 61 respondents favored follow up with MRI rather than give PCI. Medical oncologists were statistically significantly more likely to agree with omitting PCI than were radiation oncologists (p=0.022). Among all respondents, SRS was preferred for treatment of brain metastases in both PCI-naïve and PCI-treated patients.

Recent NCCN guidelines recommend PCI for LC-SCLC patients [6], if their disease is responsive to initial chemoradiotherapy. These guidelines are based on several clinical trials, which reported a lower incidence of brain metastases by 17% to 30% and improved 3-year survival by 8% to 12% after PCI [7-10]. However, these studies were conducted before introduction of MRI, which is significantly more sensitive than CT in the diagnosis of brain metastases [11]. Therefore, in some patients PCI was in fact not prophylactic, but rather a therapeutic modality for treatment of undetected brain metastases. The EORTC randomized trial showed a 13.8% survival advantage of PCI in patients with ED-SCLC, who responded to chemotherapy [20]. However, less than 30% of patients underwent brain imaging at diagnosis, and no information was provided on how many patients had brain imaging immediately prior to randomization between PCI and follow up. Furthermore, a recently reported result of a Japanese randomized study, where brain MRI was mandatory before and after randomization, showed disappearance of PCI survival benefit in patients with ED-SCLC [17]. These data reignited a controversy in the oncology community on the possibility of replacing PCI by

regular MRI-based surveillance, in order to avoid potential damage to cognitive function and other neurologic side effects of PCI.

Anatomic and pathophysiologic characteristics of radiation injury causing neurocognitive decline, related to Whole Brain Radiotherapy (WBRT) have been described in the literature. Moderate doses of radiation to the entire brain, which are common to both WBRT and PCI, are associated with white matter changes, demyelination, and vascular damage [21-23]. Cognitive disabilities in LS-SCLC patients have been well investigated in randomized RTOG 0212 and intergroup phase III studies, comparing standard and high dose PCI [24-26]. Declines of tested and self-reported cognitive function were dose dependent, but were reported in both the standard and high dose group. More of both cognitive and quality of life decline was observed in elderly patients. The RTOG 0214 randomized study directly compared PCI and MRI-based surveillance for patients with locally advanced non-small cell lung cancer [26]. Significant impairment of cognitive function was reported in the PCI group, which could strengthen the argument in favor of surveillance for brain metastasis by MRI, rather than administration of PCI for LS-SCLC as well. In addition, increased permeability of the blood-brain barrier after WBRT raises concern for severe brain damage by cytotoxic agents and other pharmaceuticals, used in close conjunction with WBRT [27-28]. Disabling neurotoxicity negating treatment benefit was reported in central nervous system lymphoma and leukemia long term survivors, treated by chemotherapy and WBRT [29-30]. The possibility of these complications should not be underestimated when considering PCI for LS-SCLC patients.

The US based survey of radiation oncologists showed lack of enthusiasm to replace PCI by MRI-based follow up for LS-SCLC [16]. However, it did not take into account randomized data showing no survival advantage of PCI vs. surveillance by MRI for ED-SCLC patients [17]. Medical oncologists were not involved in the LS-SCLC survey, thus their views were not accounted for. Our survey included 61 oncologists (both medical and radiation), practicing in 47 centers in 15 countries. Over one third (36.1%) of respondents were prepared to omit PCI in favor of MRI-surveillance, perhaps signaling a trend for a shifting treatment paradigm for LS-SCLC. Support for surveillance was significantly higher in medical as opposed to radiation oncologists (p=0.022). A randomized controlled study is required to definitively resolve the issue.

Wide availability of SRS as a salvage option for treating brain metastases can be considered as an additional reason to prefer MRI-based follow up for LS-SCLC patients. SRS with or without surgery is currently recommended for management of lung cancer patients regardless of histologic type when there is a limited number of brain metastases [31-33]. Generally, SRS for brain metastases can result in similar overall and progression free survival rates compared to WBRT, but with better preserved cognitive function [12,34]. Re-irradiation with WBRT can be particularly toxic in LS-SCLC patients previously exposed to PCI [35], and systemic therapy is of limited value for them [36]. Therefore, SRS maybe regarded as the preferred therapy for treatment of brain metastases in patients who have received PCI. Our survey revealed a strong support for the use of SRS to treat SCLC patients with brain metastases. Ongoing randomized controlled trials directly comparing SRS versus WBRT for treatment of brain metastases in SCLC patients will help to develop clear guidelines on the issue [37].

There are a number of limitations to our survey. Because of the

small sample size the results may not be representative of the entire professional oncology community. The low rate of questionnaire response could affect the survey outcome, as there may be potential opinion differences in between the professionals who completed the online survey and those who preferred not to reply. Moreover, potential variances in attitude to PCI in different countries could be underestimated because of a small respondent number per country (Table 3). Finally, there was major imbalance in the number of medical and radiation oncologists in the respondent population with predominance of medical oncologists. This difference could have led to underestimating the prevalence of views more frequently held by radiation oncologists.

Conclusion

According to the results of our survey, a substantial proportion of cancer specialists support the omission of PCI in favor of regular MRI-based follow up for patients with LS-SCLC following chemoradiation. A randomized controlled trial to determine the best approach is highly warranted.

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