Irish Journal of Medical Science (1971 -) (2019) 188:761–764
https://doi.org/10.1007/s11845-018-1912-0

REVIEW ARTICLE

Is prophylactic cranial irradiation necessary in individuals suffering from surgically resected pT1-2N0M0 small cell lung cancer?

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Received: 5 May 2018 / Accepted: 10 October 2018 / Published online: 17 October 2018
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Abstract
Adjuvant chemotherapeutics and prophylactic cranial irradiation (PCI) are both recommended in the National Comprehensive Cancer Network (NCCN) guidelines for treating individuals suffering from surgically resected pT1-2N0M0 small cell lung cancer (SCLC). Whether adjuvant chemotherapy combined with PCI is superior to adjuvant chemotherapy alone in these patients is largely unknown. PCI may therefore be with uncertain effects in surgically resected pT1-2N0M0 SCLC.

Keywords Adjuvant chemotherapy · Overall survival · Prophylactic cranial irradiation · Small cell lung cancer · Surgical resection

Introduction

Adjuvant chemotherapeutics and prophylactic cranial irradiation (PCI) were both put forward in the National Comprehensive Cancer Network (NCCN) guidelines for individuals suffering from surgically resected pT1-2N0M0 small cell lung cancer (SCLC) [1]. These treatment guidelines were developed according to clinical studies evaluating the impact of chemotherapy and PCI on SCLC patients without surgery [2, 3]. Yang et al. report the role of adjuvant therapy in a population-based cohort of patients with early-stage SCLC [4]. The results showed that the adjuvant chemotherapy was associated with significantly improved survival when compared with surgery alone. Multivariable Cox modeling demonstrated that the treatment with adjuvant chemotherapy or chemotherapy with PCI can improve the survival when compared with no adjuvant therapy [4]. It demonstrated that adjuvant chemotherapy improves overall survival (OS) for patients with pT1-2N0M0 SCLC treated with surgical resection. It is ambiguous that adjuvant chemotherapy with PCI is superior to adjuvant chemotherapy alone for patients with pT1-2N0M0 SCLC treated with surgical resection [4]. We noted that the hazard ratio was lower for the group receiving both chemotherapy and PCI at 0.52 versus a hazard ratio of 0.78 for chemotherapy alone [4], indicating that the PCI may have brought survival benefits, but there was no direct comparison between the groups. If the authors can compare these two groups, it will substantiate the value of PCI in pT1-2N0M0 SCLC treated with surgical resection. PCI improves disease-free survival as well as OS in individuals with SCLC who have a complete or partial response [2, 3]. Auperin et al.'s study refers to predominantly (but not exclusively) limited stage patients and involves patients with much more advanced disease than pT1–2 [2], whereas Slotman B et al.'s study is for extensive stage patients [3]. The benefit in surgically resected pT1-2N0M0 SCLC cannot be deduced from patients with non-surgical treatment.

Evidence supporting withholding PCI

One hundred twenty-six patients who underwent treatment with surgical resection between January 1998 and December 2009, including 32 stage I, 39 stage II, and 55 stage III SCLC cases, were retrospectively evaluated in Gong L et al.' s study. None of the patients in this cohort had received a previous PCI. Five-year survival rates in pathological stages I, II, and III were 54.8%, 35.6%, and 14.1%, respectively ($P = .001$); brain metastasis rates were 6.25% (2/32), 28.2% (11/39), and 29.1% (16/55) ($P = .026$), respectively [5]. The effect of PCI in stage I SCLC patients showing complete resection is questionable since such individuals have low brain metastasis and acceptable survival rates [5]. TNM classification was

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associated with brain metastasis [6, 7]. Meanwhile, the brain metastasis rate was shown to be significantly different in patients after complete resection compared with the value of those with incomplete resection, indicating that PCI's effects in individuals who received surgery cannot be deduced from those of patients with non-surgical treatment in SCLC. From January 2003 to December 2009, clinical data of complete resected patients diagnosed with SCLC and definitive pTNM stage based on histological evidence were retrospectively assessed in Shandong Cancer Hospital and Institute, People's Republic of China [8]. A total of 67 and 126 were enrolled in the PCI and non-PCI groups according to therapy modality, respectively; there were 49 stage I, 43 stage II, and 101 stage III cases. The results showed that PCI was associated with improved overall survival rates in individuals with surgically resected SCLC, except for the stage I disease group [8]. Further, the data from Xu et al.' s retrospective study supports using PCI in surgically resected SCLC patients with p-stage II/III disease but not in patients with p-stage I disease [9]. A large multi-institution location on stereotactic body radiation therapy (SBRT) for SCLC is consistent with the data by Gong et al. as they found that there is a low incidence of brain metastases for stage I SCLC [10, 11]. In the series by Verma et al. [10, 11], only 4 of 53 patients with stage I disease failed in the brain. Of note, median follow-up was only 18 months. Although no failures did occur in the patients who receive PCI, this frequency of failure indicates that a large number of patients would not seem to benefit from PCI. A randomized study found no enhanced OS for patients with extensive SCLC who received PCI compared to the non-PCI group; no brain metastasis was observed in these patients as assessed by magnetic resonance imaging (MRI) [12]. Thin cut stereotactic MRI imaging should be used for surveillance, as this imaging has greater sensitivity and is using the current hippocampal-sparing trial for SCLC patients [13]. Early trials did not always use MRI for brain metastasis detection. In stage I SCLC patients not receiving PCI, surveillance for metastasis by brain imaging should be considered. Acute effects including leg weakness, nausea/vomiting, and anorexia from PCI should be noticed [3]. Furthermore, acute and chronic neurotoxicity should be taken into consideration in individuals being administered PCI, since excellent prognosis can be obtained in surgically resected pT1-2N0M0 SCLC patients [2, 14–16]. Therefore, the role of PCI in such patients who received adjuvant chemotherapy remains unclear.

Evidence supporting PCI

There is some evidence supporting PCI in surgically resected stage I SCLC. While evaluating 156 SCLC cases receiving a surgical treatment in a multicenter trial (66 IA and 29 IB cases), multivariate analysis showed longer OS in individuals who underwent PCI [17]. PCI was only given to 13 of the 156 patients. This was a retrospective study in which only about two thirds of patients were stage I, and the findings may not reflect all possible stage I cases. In another study, 39 SCLC patients of stages pT1/pT2 and pN0/pN1 received tumor resection and systematic lymph node dissection were retrospectively analyzed. Among them, 16 and 21 cases underwent adjuvant thoracic radiotherapy and PCI, respectively. Interestingly, the patients who received PCI have a significantly improved brain

Table 1 Clinical studies about PCI in SCLC patients which received surgery

Author (ref.)	Character of study	Study population	Treatment	No. of patients	Results
Gong L et al. [5]	Retrospective study	SCLC patients with surgical resection for stages I–III	No PCI	126 (stage I 32)	5-year survival and brain metastasis rates of 54.8% and 6.25%, respectively, were obtained in cases with pathological stages I.
Zhu H et al. [8]	Retrospective study	Completely resected patients with pTNM stages I–III	PCI vs without PCI	193 (stage I 49)	PCI can improve overall survival, except for stage I disease.
Xu J et al. [9]	Retrospective study	Completely resected patients with pTNM stages I–III	PCI VS without PCI	349 (stage I 78)	Support using PCI in patients with p-stage II/III disease but not in patients with p-stage I disease.
Yokouchi H et al. [17]	Retrospective study	Surgically resected SCLC patients	PCI vs without PCI	156 (stage I 95)	Patients who underwent PCI had longer overall survival.
Bischof M et al. [18]	Retrospective study	Patients in stages pT1/pT2 and pN0/pN1 who underwent tumor resection and systematic lymph node dissection	PCI vs without PCI	39 (T1-2N0M0 24)	PCI improved brain metastasis-free survival and overall survival.

metastasis-free survival and OS compared with the non-PCI group [18]. This was also a retrospective study with a small sample and not all patients were pT1-2N0M0, indicating that the role of PCI in surgically resected pT1-2N0M0 SCLC remains uncertain.

The role of PCI in pT1 and pT2

The 8th edition of AJCC staging defines T2b as up to 5 cm in size, which used to be T2a under the 7th edition as the 7th edition defined T2b as between 5 and 7 cm [19]. Both editions describe T2b disease as stage IIA. Although current NCCN guidelines (which employs AJCC 8th edition staging) describe resected T1–T2 as those who should be considered for PCI, T2b under the 8th edition would define those patients as stage IIA, under the 7th edition relevant to the referenced publications, up to 5 cm would be T2a and those patients would be stage I as analyzed by the authors. All of the published data is according to the 7th edition of AJCC staging [5, 8–11], that is to say, patients with pT2a is not be subdivided into "pT2a ($3 < \text{tumor size} \leq 4$ cm)" and "pT2b ($4 < \text{tumor size} \leq 5$ cm)" under the current 8th edition of staging criteria. And most of them demonstrated that stage I (tumor size <5 cm) cannot benefit from PCI. It means that patients with pT1–2 (tumor size < 5 cm) according the 8th edition of AJCC staging cannot benefit from PCI. Five-year survival rates in pathological stage II was much lower than stage I; brain metastasis rate in pathological stage II was much higher than stage I according to the 7th edition of AJCC staging [5]. The patients of T2b according to the 7th edition may benefit from PCI. But there are no related data about the rate of brain metastases in patients receiving PCI or not.

Conclusion

The number needed to treat (NNT) may be very high in preventing brain metastases for early-stage patients. Gong L et al.' s study and Verma V's studies suggested that the incidence of brain metastases in pT1–2 patients may be around 5–6% [5, 10, 11]. Based on the Auperin et al. series, the HR for decreasing brain metastases with PCI is 0.46, meaning the risk is about cut in half [2]. Therefore, the absolute benefit is on the order of 3%, corresponding to a NNT of 34. Assuming active surveillance would catch some patients before the metastasis becomes a problem would increase the NNT even further. This indicated the value of PCI might be relatively low. When presented with the data of the risks and benefits specifically noting the likelihood of at least short-term side effects and the potential for long-term cognitive dysfunction and the high number of patients that would need to be treated to achieve a benefit in either brain control or survival, we would expect many patients would choose to avoid PCI. Of note, the Alliance cooperative group is launching a study of active surveillance for both limited- and extensive-stage patients. It should be emphasized that shared decision-making is essential for PCI option for patients, and the exact incidence of metastases appears to be low and therefore the expected benefit in most patients is questionable. Clinical studies about PCI in SCLC patients which received surgery are listed in Table 1. In conclusion, the recommendation based on evidence and consensus of PCI in surgically resected pT1-2N0M0 (AJCC 8th edition staging) SCLC should not be category 1; category 2B may be more suitable.

Funding This work was supported d by the Zhejiang Provincial Natural Science Foundation of China (No.LY15H290001).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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