Introduction

Since many cytotoxic or cytostatic drugs that were used in the treatment of acute lymphoblastic leukemia (ALL) did not adequately cross the blood-brain barrier, prophylactic cranial irradiation (PCI) was introduced in the 1960s to target the subclinical leukemic residuals in the central nervous system (1). PCI led to a substantial improvement of disease-free survival (DFS) and overall survival (OS), yet has on the long run become nearly fully replaced by (long-term) intrathecal chemotherapy (ICT) without affecting DFS and OS (2). The rationale behind the change of modalities was not established quickly, but has rather evolved on the basis of long-term follow-ups, in which late radiation-induced toxicities including neurological and neurocognitive impairments, hormone deregulation, and secondary cancers appeared in high frequencies especially in pediatric patients (3-7).

To date, only few indications for PCI in adult and childhood leukemia exist. It is still applied in childhood AML (8) as well as in childhood ALL if the risk for relapse is high or if patients do not adequately respond to chemotherapy (9). In adults, PCI is performed in highly aggressive (Philadelphia-chromosome positive) ALL, for example in the GMALL PH-01 study as part of the induction therapy (EudraCT 2010-022854-18).

For small-cell lung cancer (SCLC), PCI was included in standard regimens for limited disease (LD) patients in the early 1980s, where it was clearly shown that it efficiently reduced the 2-year occurrence rate of brain metastases (BM) from 58% to 11% (10). PCI also showed to improve OS of patients in complete remission (CR), as impressively demonstrated in a meta-analysis of seven individual trials from 1977-1994 by Aupérin and colleagues (11). Furthermore, the EORTC multicentre randomized phase

Review Article

Potential toxicities of prophylactic cranial irradiation

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Abstract: Prophylactic cranial irradiation (PCI) with total doses of 20-30 Gy reduces the incidence of brain metastasis (BM) and increases survival of patients with limited and extensive-disease small-cell lung cancer (SCLC) that showed any response to chemotherapy. PCI is currently not applied in non-small-cell lung cancer (NSCLC) since it has not proven to significantly improve OS rates in stage IIIA/B, although novel data suggest that subgroups that could benefit may exist.

Here we briefly review potential toxicities of PCI which have to be considered before prescribing PCI. They are mostly difficult to delineate from pre-existing risk factors which include preceding chemotherapy, patient age, paraneoplasia, as well as smoking or atherosclerosis. On the long run, this will force radiation oncologists to evaluate each patient separately and to estimate the individual risk. Where PCI is then considered to be of benefit, novel concepts, such as intensity-modulated radiotherapy and/or neuroprotective drugs with potential to lower the rates of side effects will eventually be superior to conventional therapy. This in turn will lead to a re-evaluation whether benefits might then outweigh the (lowered) risks.

Key Words: Prophylactic cranial irradiation (PCI); potential toxicities; brain metastasis (BM); small-cell lung cancer (SCLC); non-small-cell lung cancer (NSCLC)
III trial showed that even patients with extensive disease (ED)-SCLC will benefit from PCI with respect to DFS and OS if they showed any response to chemotherapy (12).

In contrast to the beneficiary effects in SCLC, PCI has failed to improve OS rates in non-small-cell lung cancer (NSCLC) in multiple randomized clinical studies (13-16). Additionally, since the relapse rates with brain as first site have not changed after application of PCI (17,18), it is currently omitted in NSCLC treatment regimens.

There is controversy about how precisely one may delineate PCI toxicity from disease- or treatment specific toxicities that are present a priori or that will (co-)elicit side effects of the irradiation. We will briefly introduce current dose regimens and review toxicities that, from our clinical experience, are the commonly experienced ones during and after PCI.

**Technical implementation and doses**

To date, PCI is commonly initiated within 4-6 weeks after chemotherapy using bilateral, parallel opposing fields with high energy (megavoltage) photons (doses are commonly specified to the midline), whereas each field is treated daily on a 4-5 times per week schedule. Depending on the underlying disease, the total doses range from 12 to 36 Gy.

As a part of the treatment for childhood ALL, early PCI regimens consisted of doses of 12-24 Gy and long-term studies found that the dose can be safely reduced without any loss of effectivity (19). The DFCI Consortium protocol includes PCI with 12 Gy in two daily fractions of 0.9 Gy concomitant with double ICT for standard-risk patients (20). For patients with high risk ALL, the AALL0232 study protocol foresees PCI with 12 Gy in 8 fractions only for slow early responders without manifest CNS involvement (9).

Due to the variety of different findings there is still uncertainty which dose might be optimal for SCLC. It is believed from dose-response analyses that at least 30-36 Gy, applied in 2 Gy-fractions are most likely needed to eliminate cranial metastasis (21) and that doses below 30 Gy have no effects (22). A meta-analysis in 1998 analyzed 7 different regimens for PCI and found the lowest hazard ratio for 36 Gy in 18 fractions (23). The younger RTOG 02 12 trial also addressed this question and randomly assigned LD-SCLC patients to PCI with the standard dose (arm 1) of 25 Gy in 10 fractions or in an arm using higher doses (arm 2) of 36 Gy in 18 or 24 fractions (24). The study showed no difference in the incidence of BM when comparing high to low dose PCI but a significant increase in mortality when higher doses were given. For ED-SCLC, in contrast, the 2007 EORTC trial showed comparable benefits and toxicities when using 20 Gy in 5-8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions and 30 Gy in 10 or 12 fractions (12).

A commonly applied dose for PCI in the past NSCLC studies was 30 Gy in 15 fractions (13,14,25). In the SWOG study, the first patients that were recruited were treated with 37.5 Gy in fractions of 2.5 Gy which led to an increased death rate, prompting the committee to reduce the dose 30 Gy in 2 Gy fractions for all further patients (26).

**Toxicity**

Prophylactic and, even more, therapeutic irradiation of the brain may be accompanied by early and late side effects. Early side effects may be reversible and appear during PCI or slightly delayed within few weeks after the end of radiotherapy. A first classification of the temporal occurrence of radiation-related toxicities was done by Sheline and colleagues in the 1980s (27), in which acute and subacute radiation reactions of the brain at around four months were distinguished from delayed irreversible impairments months or years after completion of cranial radiotherapy (Table 1).

In a prospective study on 44 patients with and without BM...
our group evaluated very early effects (tests were performed before PCI, during PCI and 6-8 weeks after PCI) of PCI on neurocognition. Our analysis has shown that in contrast to therapeutic cranial irradiation (TCI), PCI does not considerably impair cognitive functions after 1-3 fractions of irradiation (28). In contrast, 6-8 weeks after PCI, patients scored significantly lower on verbal memory as compared to a control group receiving radiotherapy to the breast (28). Of note, 44% of patients that received PCI showed a decline of at least one verbal memory subtest and, at this time point, patients that received PCI scored similarly to patients that received TCI. However, there is still uncertainty about how this rate correlates to a much higher rate of CNS demyelination (60-100%) that can be seen months to years after PCI (Figure 1) (29).

The incidence of toxicities are likely dependent on certain a priori risk factors, including age, preceding or concomitant chemotherapy and other putative risk factors that are to date not exactly defined as such (i.e. smoking and/or atherosclerosis). The most evident risk factor for developing side effects is age: since the developing brain is much more sensitive to irradiation than the adult brain, PCI in children leads to high rates of acute and late toxicities (30-32). An early effect after PCI in children has been observed in an ancient report of Freeman and colleagues, who noted abnormal behavioural patterns in patients with ALL. In detail, more than two thirds of the children showed somnolence, anorexia, and lethargy at around 6 weeks after PCI (33). Interestingly, all symptoms were transient and completely resolved spontaneously, fully consistent with later investigations which showed that a transient demyelination of CNS nerve fibres is the underlying cause (34). The complex mixture of symptoms with somnolence being the chief complaint lead the community to dub this early PCI toxicity “somnolence syndrome” (35). The syndrome does not seem to be dose-dependent and has to date appeared at fairly any dose between 18 and 24 Gy (36). It was even described to occur 6 weeks after total body irradiation (TBI) with 12 Gy before bone marrow transplantation (37). Although the somnolence syndrome was also described to transiently occur in adults (38), neurotoxicity after TBI remains extremely rare. In a prospective study by our group, we followed 58 patients that underwent hyperfractionated TBI (14.4 Gy in 12 fractions)

![Figure 1](image1.png)  
Radiation-induced leukoencephalopathy. Shown is a T2-weighted MRI scan 8 weeks and 7 months after irradiation showing an increased symmetric hyperintensity of the cerebral white matter.
before bone marrow transplantation and saw no impairment in any of the applied neuropsychological tests (the median follow up was 27 months) (39).

An important aspect of PCI toxicity in children is temporary or permanent hormone dysfunction. It is to date not clear whether the pituitary gland, the hypothalamus or both are affected by irradiation. However, early studies showed that hypopituitarism is dose depended, whereas lower doses (in the range of 12-24 Gy) seem to solely induce growth hormone (GH) dysfunction (40,41). The GH axis is the most vulnerable axis and impairment represents a major concern when prescribing PCI for (pubertal) children. Of note, adult patients easily compensate GH deficiency (42). At higher doses (including those used for PCI, e.g., 30-36 Gy) TSH secretion is found impaired in nearly 30% and may remain disturbed long-term in up to 9% of patients (43,44). It is well known that in this case secondary hypothyroidism will not only result in somatic disorders but also cause neuropsychiatric symptoms such as mood changes or depression. If left untreated (or undetected long time after PCI) cognitive functions will be affected and patients will show impaired executive functions and poor learning capabilities (45).

Caution is advised when diagnosing PCI toxicity in adults, as many of the “classical” PCI toxicity data is derived from studies on SCLC, where patients primarily undergo chemotherapy which is followed by PCI. The influence of chemotherapy on cognitive functions of many cancer patients, often referred to as “chemo-brain” or “chemo fog” remained underestimated for a long time (46). Largely similar to the side effects evoked by cranial irradiation, it is not surprising that the effects were rather attributed to the radiation than to chemotherapy (47). However, already more than a decade ago, it has been noted that patients receiving adjuvant (standard-dose) chemotherapy for breast cancer exhibit decreased cognitive functions (memory and language) as compared to matched control groups (48). In a prospective study by Komaki et al., SCLC patients that finished initial therapy were asked to perform neuropsychological tests before and after PCI (49). Although the authors saw a slightly significant decline of executive function and language after 1 year (which turned insignificant in later tests), they noted that roughly half of patients have neurocognitive deficits before PCI (49). Logically, highest toxicity rates were observed in studies where chemotherapy was concomitantly applied with PCI: a simultaneous low dose concurrent chemotherapy during PCI will result in abnormal neuropsychological tests in nearly one half of all treated patients with SCLC (median follow-up ~6 years) (50). Nowadays it is accepted that chemotherapy alone induces white matter changes especially in the frontal, parietal and occipital lobes, consistent with the notion of chemotherapy-related axonal degeneration and demyelination (51,52). Of note, there is evidence that associated cognitive deficits persist for more than 10 years, which can overlay most (if not all) PCI-induced toxicities (51).

Another confounder that has to be considered when diagnosing PCI toxicity is the broad variety of possible paraneoplastic syndromes, which may even be manifesting prior to the underlying lung cancer, or its recurrence, respectively (53). Especially patients with SCLC may present with CNS-involving paraneoplasias, such as subacute sensory neuropathy, mononeuritis multiplex, Lambert-Eaton myasthenic syndrome, encephalomalacia or necrotizing myelopathy (54). Although the etiologies are currently not clear, it is discussed whether paraneoplasias may resemble a classical autoimmune disease with the presence of “onconeural” antibodies (55). CNS-involving paraneoplasia leads to impaired neurocognitive functions, including memory loss, distractibility, fatigue or mood disturbances (56), which are symptoms that are highly similar to those induced by PCI.

Beside residuals of the preceding chemotherapy and paraneoplasia, other factors have to be mentioned that may elicit PCI toxicities. “Baseline” pathologies such as undetected micrometastases, long-term smoking effects or other age-related abnormalities may flare up in patients during treatment. It is even possible that one condition or therapy may increase the toxicity of another: more than two decades ago Johnson et al. studied long-term survivors of SCLC and saw that CT-morphological (ventricular dilatation and cerebral atrophy) abnormalities and impaired neurocognitive effects are more frequent when chemotherapy was concurrently applied (50). Similar conclusions were drawn later by other groups (57-59). Another example might be that age per se can display a risk factor for late effects after PCI since the irradiated brain ages faster and is at risk for early onset dementia (60). In line with this, the RTOG 02-12 study (see above) detected higher age to be the most predictive risk factor for PCI toxicities (61). Of note, it is known since the early 70s that a pre-existing vascular damage is accelerated by radiation (62) and assuming that more than 95% of all SCLC/NSCLC patients are smokers, a possible underlying cause of this age-related PCI toxicity may be the higher incidence of hypertension and/or (cerebral) artherosclerosis in these.
patients.

As many of the patients receiving PCI have a more or less reduced life expectancy, the remaining quality of life (QoL) probably displays one of the most important measures for clinical decision making. For SCLC, QoL after PCI has been assessed in three randomized controlled trials, whereas two of which showed no significant differences between patients receiving PCI and controls (22,61). In the EORTC trial, Slotman and colleagues defined six QoL end points: global health status, hair loss, fatigue, and role, cognitive and emotional functioning. Although baseline scores were similar in both arms, a significant decline of QoL due to hair loss and fatigue (at 6 weeks and 3 months) was observed in patients receiving PCI (63). It has to be noted for completeness that there was no evidence for reduced QoL after PCI in patients with advanced-stage NSCLC (16).

**Novel concepts avoiding PCI toxicities and putatively new indications**

More work will be necessary to further delineate the influencing factors that may contribute to PCI toxicities. To start with, the optimal dose and fractionation schedule for PCI should soon be clearly defined as this question is a part of ongoing studies (e.g., for SCLC in RTOG 02-12). Novel techniques to avoid known adverse effects at any dose will also be required as part of a new concept aiming at improving the therapeutic ratio of PCI. With the advent of highly-conformal intensity-modulated radiotherapy (IMRT), organs at risk such as the hippocampus and scalp may be better spared.

The RTOG 0933 trial aims to find out whether sparing of the hippocampus during cranial irradiation may lower the incidence of radiation-induced neurocognitive toxicity. The rationale behind this trial is that the hippocampus is rarely affected by BM but displays the major site of learning, memory and spatial information (64). In one of the initial feasibility studies exploring IMRT for PCI, the mean doses to the hippocampus could be reduced by 81-87% to doses of 0.49-0.73 Gy with preserved target volume coverage and homogeneity (65).

Given that IMRT may also be used to prevent permanent hair loss, which significantly decreases QoL of both female and male cancer patients (66-69) and (as stated above) also decreases QoL after PCI (63). Roberge et al. were among the first to show the possibility to reduce doses on the scalp. They validated their alopecia-avoiding whole brain radiation therapy plans with thermoluminescent dosimetry and showed that the median dose to the scalp can be reduced by nearly 40% without affecting target volume doses (70). Although this does not prevent transient alopecia in most of the treated patients, it may be of benefit for those with a priori risk factor for increased alopecia (e.g., previous or concomitant chemotherapy).

However, assuming that IMRT might not be available to every radiation oncologist, the use of neuroprotective drugs before and/or during PCI might be an option. Several drugs are currently studied that may protect the CNS from irradiation damage, whereas the most promising data were obtained for peroxisome proliferator-activated agonists, angiotensin-converting enzyme inhibitors and angiotensin type-1 receptor blockers, which have shown to ameliorate radiation-induced injuries in vivo (71).

In the light of potentially reduced toxicities of future PCIs, one may now have to re-evaluate whether there are patient collectives that are at risk for BM but currently do not receive PCI due to toxicity. The key studies that evaluated PCI toxicity analyzed patients of stage IIIA/B, that resemble a collective of lymph node positive, non-metastatic patients with diverse non-small-cell entities (13-16). It is known from early studies in the late 1980s that especially nonsquamous-cell (NSq) carcinomas strongly tend to metastasize to the brain (72) and retrospective analyses and necropsies have revealed that roughly 50% of NSq patients will experience BM (73-75). On the way to find a subgroup in the NSq group that might benefit from PCI, it is important to mention that tumor size and lymph node status are the key determinants for assessing the risk of BM in NSCLC (76,77). In this regard, a very recent analysis by Ding and colleagues revealed that nearly 60% of patients with NSCLC stage IIIA-N2 developed BM within 5 years if more than 30% of all excised lymph nodes were affected (78). If less than 30% were affected, they saw that roughly 30% of patients had BM. Their data suggest that patients with NSq-NSCLC with N≥2 and >30% affected nodes might benefit from PCI. Consequently, it should now be tested if the (putatively) low toxicities of novel PCI-treatment modalities (such as IMRT) could provide a benefit to this subgroup.

**Conclusions and outlook**

It is well documented that PCI reduces the incidence of BM and improves overall survival of patients with LD-SCLCL and of patients that showed any response to chemotherapy in ED-SCLC. With the advancement of novel anticancer-
therapies, more and more patients that require PCI will survive long term, which will require new approaches to prevent toxicities. Concurrent or preceding chemotherapy as well as higher age are co-impairing cognition in patients receiving PCI, which should be considered in clinical decision making. In the future, novel concepts of prophylactic and therapeutic whole-brain irradiation have to be established for these patients. The techniques will include hippocampus-sparing and scalp-sparing highly conformal prophylactic cranial intensity-modulated radiotherapy (IMRT). Prospective studies will then have to prove similar efficiency as conventional PCI. Finally, assuming reduced rates of future PCI, new studies will have to be set up to re-evaluate whether patients with NSq-NSCLC that are at high risk for BM may eventually benefit of PCI.

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