Prophylactic cranial irradiation: recent outcomes and innovations

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Practice Points

- Prophylactic cranial irradiation (PCI) draws historically from experience in the treatment of the CNS as a sanctuary site of childhood leukemia.
- Small cell lung cancer (SCLC) represented a logical leap to a disease well known to frequently and rapidly metastasize to the CNS.
- PCI has proven to improve both brain metastasis rates as well as overall survival in SCLC.
- PCI reduces brain metastasis in non-small-cell lung cancer, but as yet, has failed to demonstrate an overall survival benefit. Many of the more recent trials in the arena have failed to accrue or directly address this issue.
- As whole brain radiotherapy (WBRT) techniques and medical management improve, the role for PCI may expand.
- Hippocampal avoidance WBRT as well as memantine use in the WBRT setting represent promising techniques for reducing toxicity associated with PCI.
- PCI's role in other malignancies, such as breast cancer, remains controversial.

SUMMARY Brain metastases represent a frequent problem in several malignancies. They can shorten survival while causing significant morbidity and impairment in the patient's quality of life. Prophylactic cranial irradiation (PCI) has become an integral part of the standard of care in small cell lung cancer (SCLC), yet its role in other malignancies remains the subject of significant discussion. Its role has been extensively investigated in non-small cell lung cancer and less so for breast cancer and other malignancies. Improvements in medical care as well as in whole brain radiotherapy (WBRT) techniques may improve the risk-benefit ratio of this therapy so as to expand its role in cancer care. The use of memantine in WBRT patients as well as the use of hippocampal avoidance techniques are of particular interest in this effort. Herein, we review the history of PCI, its current use, and areas of investigation in the application of PCI.

CNS involvement remains a common cause of significant morbidity and mortality among a number of malignancies. As such, a number of approaches have been employed in the treatment of this region immediately following diagnosis or early in the course of disease to eradicate micrometastatic deposits, a strategy referred to as 'prophylactic therapy'. Prophylactic cranial irradiation (PCI) arose as a modality for addressing such residual micrometastatic CNS disease in childhood leukemia [1]. The

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similarities in principle between the treatment of leukemia and that of small cell lung cancer (SCLC) were quickly realized. SCLC, much like leukemia, represents a malignancy that is often widespread at diagnosis with systemic involvement. Treatment of each involves an aggressive chemotherapy regimen to which the disease profoundly, and often completely, responds, and this degree of treatment effect extends to radiotherapy as well. Due to the blood–brain barrier, many systemic therapies fail to reach CNS disease or do so at sublethal levels. Radiotherapy, therefore, represents a particularly suitable methodology for treating micrometastatic disease at this sanctuary site. It should be noted that PCI is actually a misnomer in the sense that its purpose is to treat clinically inapparent disease and not to specifically act as prophylaxis against future metastasis.

The comparison to leukemia led to the consideration and study of the role that PCI may play in lung cancer [2]. The importance of addressing the CNS in SCLC has become more evident as improved imaging has revealed that approximately one in six patients presents with asymptomatic brain involvement [3]. Additionally, the devastating effect upon quality of life and survival that brain metastasis portends raises the stakes of untreated disease of this site. Despite palliation with whole brain radiation (WBRT) among other therapies, up to half of patients still succumb secondary to intracranial progression with the vast majority of patients surviving only 3–7 months [4].

Relapse in the form of brain metastasis continues to be a common occurrence despite advances in therapy. As survival has improved, the high incidence of CNS metastasis in SCLC has become clearer with close to 60% of patients failing in this manner without PCI at 24 months from diagnosis [5]. Autopsy data indicate that the clinical incidence underestimates the actual rates of disease [6]. These rates concur with the extrapolation of clinical trial data as well. Due to these overall very poor outcomes, PCI, though it is certainly not without risks, has been deemed likely to be and has proven to be of significant benefit in well selected patients with SCLC.

More recently, the role of PCI has begun to logically expand to non-small-cell lung cancer (NSCLC). Brain metastasis remains a common outcome of NSCLC with approximately one-third of those receiving therapy eventually being diagnosed with brain lesions [7,8]. The

occurrence of this is very early, with 22.5% diagnosed during treatment and 46.5% in the first 4 months from diagnosis [9]. Consequently, clinical trials of PCI in NSCLC have gained increasing acceptance and interest.

In this review, we intend to address the current role of PCI especially in the setting of lung cancer. However, we also will touch upon the broadening role that this therapy may have going forward. Advances in technique such as hippocampal sparing WBRT may improve the risk-benefit ratio of PCI and thus aid in the expansion of its use. Ultimately, we will propose future avenues in other malignancies where PCI is being considered.

SCLC

• Limited Stage

Not only is the incidence of brain metastasis at time of diagnosis high among patients with SCLC, but the risk of CNS relapse over time is also very high. It has been estimated that without PCI, intracranial failure occurs in 67% of patients by 2 years [10]. This includes 45% of patients who have brain metastasis as their first and only site of relapse [10]. Initially, with the assumption that reducing these devastating rates of CNS involvement would show clear benefit, multiple randomized trials studied PCI in all-comers regardless of the state of their primary or extracranial disease. This approach was intuitive considering the significant morbidity and high-percentage cause of death that brain metastasis carries. Such trials predominated in the 1980s, but while demonstrating a significant benefit in the reduction in brain metastasis, they failed to show a clear survival benefit [11]. These findings have rightfully been attributed to the heterogeneity of the studied population. Without controlling for the response to initial therapy, the survival of patients could easily have been affected more heavily by competing causes of death from systemic progression of disease.

By the early 1980s, it became clear that complete responders to initial therapy might demonstrate a survival benefit from PCI [12]. Pursuant to this line of thinking, six published randomized trials, summarized in [Table 1](#), followed to evaluate PCI specifically in complete responders [10,13–17]. Each of these trials showed a clear reduction in brain metastases, but survival differences were too small to statistically detect in these underpowered trials. Auperin *et al.* conducted a composite meta-analysis

Table 1. Published randomized trials evaluating the role of prophylactic cranial irradiation in small cell lung cancer.

Trial	Years	Patients (n)	PCI dose (Gy/# of fractions)	Brain metastasis rate (%) (PCI vs no PCI)	p-value	Survival (PCI vs No PCI)	p-value	Ref.
UMCC	1977–1980	29	30/10	0 vs 36	0.02			[13]
Okayama	1981–1986	46	40/20	22 vs 52	<0.05	Median 21 months vs 15 months	0.097	[14]
PCI-85	1985–1993	300	24/8	40 vs 67 (2 year rate)	<10 ⁻¹³	29 vs 21.5 (2 year)	0.14	[10]
UKCCCR-EORTC	1987–1995	314	Variable	38 vs 54 (3 year rate)	0.00004	21 vs 11 (3 year)	0.25	[16]
PCI-88	1988–1994	211	Variable	44 vs 51 (4 year rate)	0.14	22 vs 16 (4 year)	0.25	[17]
ECOG-RTOG	1991–1994	32	25/10	24 vs 53	NS	Median 15.3 months vs 8.8 months	0.25	[15]
Auperin Meta-analysis	1977–1995	987	Variable	33.3 vs 58.6 (3 year rate)	<0.001	20.7 vs 15.3 (3 year)	0.01	[18]

PCI: Prophylactic cranial irradiation.

including nearly 1000 patients, demonstrating statistically significant absolute overall survival benefit of 5.4 and 8.8% at 3-year follow-up in limited and extensive stage disease, respectively; further, PCI halved the incidence of CNS relapse [18]. This finding in patients with a complete response fits well with the clinician's goals of therapy. If the patient's overall disease is poorly controlled, there is clearly little benefit to subjecting the patient to the side effect profile associated with PCI. Included in this meta-analysis were primarily patients with limited stage disease though extensive stage patients were also included. These results have subsequently been reproduced in both retrospective Surveillance, Epidemiology, and End Results (SEER) Program data and further meta-analysis [19,20]. This more extensive meta-analysis, including over 1500 patients, demonstrated a statistically significant overall survival improvement with a hazard ratio of death of 0.82 for the PCI patients and again a halving of brain metastasis incidence [20].

• Cognitive outcomes after PCI in limited stage SCLC

A number of retrospective studies have raised concerns regarding neurotoxicity after PCI, but these studies have been compromised by many factors. Most importantly, they have been challenged by a lack of baseline neuropsychological testing as prospective cognitive studies have shown up to 97% of limited stage SCLC patients have evidence of cognitive dysfunction prior to PCI [21,22]. Two of the largest randomized trials of PCI incorporated prospective neuropsychometric testing, and both found a significant proportion of patients had cognitive dysfunction at baseline. Yet, they found no differences in cognitive performance between the randomization

arms of PCI or no PCI [10,16]. However, higher doses of PCI are associated with worse cognitive outcomes as a randomized trial of different radiation schedules found greater rates of cognitive decline in patients treated with 36 Gy compared with patients treated with 25 Gy [23].

This finding was also borne out in the intergroup randomized study which included 720 patients with limited stage SCLC. Due to the concern that the optimal PCI dose for maximum control of brain metastasis with minimum side effects had yet to be established, this effort set out to compare two doses with three fractionation schedules. Patients either received 25 Gy in 10 daily fractions, 36 Gy in 18 daily fractions, or 36 Gy in 24 twice daily fractions. There was no difference in the incidence of brain metastases between the arms though mortality was higher in the high dose group, likely secondary to increased cancer-related mortality [24]. As such, 25 Gy remains the standard of care for PCI delivery.

Gondi *et al.* recently analyzed RTOG 0212 and 0214, and demonstrated a decline in Hopkins Verbal Learning Test (HVLT) Recall and self-reported cognitive functioning in patients undergoing PCI versus those who were observed, though these effects were not closely correlated [25].

Because the potential for neurotoxicity from a therapy specifically directed at preserving neurologic function, with only a small survival benefit, is a real concern, Lee *et al.* have developed a useful decision analysis process that further demonstrates the advantages of PCI in limited stage SCLC patients [26]. However, this model also clearly brings into question the role of PCI should survival rates in SCLC change substantially. Approaches that lower neurotoxicity may

become all the more important if SCLC survival rates improve, and the approaches discussed below could become relevant in this context.

• Extensive stage

Auperin *et al.* noted in their meta-analysis that there was a small subset of patients with extensive stage disease who experienced improvement in overall survival on par with limited stage patients [18]. However, this cohort represented less than one-fifth of those enrolled, and therefore the results did not gain widespread clinical acceptance.

In practice, most patients present with extensive stage disease. In fact, the proportion of patients with extensive stage disease at diagnosis has risen over the last 40 years, likely secondary to improved imaging for initial staging. While systemic therapy has improved short-term survival rates, long-term control of the disease has remained elusive. Despite numerous advances, the 2 year survival rates for extensive stage disease rose from 1.5 to only 4.6% in the period between 1973 and 2000 [27]. As mentioned above, salvage therapy for these patients has limited success.

In 2007, the European Organization for Research and Treatment of Cancer (EORTC) set out to more directly address the role of PCI in extensive stage disease [28]. They enrolled a broader range of patients according to their response to therapy. Instead of a complete response, any response as defined by the participating center made the patient eligible for PCI. Extensive stage was defined similarly to the traditional definition of disease outside a single radiation portal. Supraclavicular disease or pleural effusions were acceptable for inclusion. The primary objective was to identify possible reduction in symptomatic brain metastases. Several fractionation schedules were permitted including 20 Gy in five fractions, 20 Gy in eight fractions, 25 Gy in ten fractions, 24 Gy in 12 fractions, 30 Gy in 12 fractions, or 30 Gy in ten fractions.

The hazard ratio for symptomatic brain metastases for the PCI group, relative to the control arm, for patients with extensive stage disease was a profound 0.27, implying a 73% reduction in risk [28]. This also translated to an improvement in disease-free survival. More impressively, there was also benefit in terms of overall survival, with a hazard ratio for death of 0.68, in favor of the PCI arm [28]. This equated to an actuarial

improvement in the 1 year survival rate from 13.3% for the control group to 27.1% for the PCI cohort [28].

Quality of life assessments were performed at up to 9 months out from therapy, and these demonstrated moderate increases in fatigue, hair loss, appetite changes, nausea/vomiting, and leg weakness in the PCI cohort. However, these were quite tolerable compared with the morbidity of brain metastasis [28]. The primary criticism of this study was its lack of mandatory pre-treatment brain MRI in asymptomatic patients which may have led to inclusion of patients who may have harbored asymptomatic brain metastases. If these patients were randomized to the PCI arm, the cranial radiation could in fact have acted in more of a therapeutic manner, whereas the control cohort patients would have not received any effective therapy for this, and hence could have rapidly progressed from unknown asymptomatic brain metastases to 'intracranial failure'. Nevertheless, PCI has become the standard of care in these patients [29].

More recent confirmatory evidence for these results comes from a pooled analysis from the North Central Cancer Treatment Group, who examined patients with extensive and limited disease with at least stable disease following chemotherapy and thoracic radiotherapy. This 318 patient analysis demonstrated improvement in survival (at 1 and 3 years) with limited toxicity using traditional fractionation schedules [30].

NSCLC

Considering the high rate of brain metastasis following conventional chemoradiotherapy, locoregionally advanced NSCLC represents a logical disease in which the role of PCI should be examined. Improvements in therapy for this disease have led to modest increases in survival and local control. The lifetime risk for developing brain metastasis in locally advanced NSCLC is estimated to be more than 40% with upwards of one-third failing first in the brain [31]. PCI has therefore been evaluated in these patients.

• Randomized controlled trials of PCI in NSCLC

There is clear level 1 evidence to suggest that PCI decreases the subsequent incidence of brain metastasis in locoregionally advanced NSCLC, but not survival.

The Veterans Administration Lung Group was the first to test PCI in a randomized manner

for NSCLC [32]. This 1981 study, included 281 patients with inoperable NSCLC who were randomized to either 50 Gy in 25 fractions to their lung disease or a 'short course' of 42 Gy in 15 fractions. They were secondarily randomized to PCI with 20 Gy in ten fractions or observation. There was a decrease in the 2-year rate of clinically detected brain metastasis in the NSCLC group from 13 to 6% with a p-value of 0.038 [32]. The limitations of this study included its small size, low dose of PCI, and heterogeneous chemotherapeutic regimens.

In 1984, Umsawasdi *et al.* reported on a small randomized study of NSCLC patients who had completed chemoradiotherapy with CAP (cyclophosphamide, doxorubicin, and cisplatin) or chemotherapy alone [30]. Patients were randomized to observation or PCI (30 Gy in ten fractions) if they were without clinical evidence of disease following initial therapy. This study did include a small percentage of patients with Stage I and II disease. The rate of CNS metastasis decreased from 27 to 4% ($p = 0.02$) [33]. With only 97 evaluable patients, this study was not powered to detect a survival advantage.

In a 1991 RTOG study, a clinically meaningful (from 19 to 9%), but non-significant reduction in brain metastasis was noted [34]. A total of 187 patients with Stage II and III NSCLC were included, and a non-significant reduction in survival was realized in the PCI group. In a Southwest Oncology Group (SWOG) study, 254 patients were randomized with 226 evaluable patients, each with inoperable Stage III disease [35]. Following randomization to either definitive radiotherapy or chemoradiotherapy, patients were randomized to PCI or observation. Again there was significant ($p = 0.003$) reduction in brain metastasis in the PCI group (1%) versus the observation arm (11%).

Recently, the RTOG published a Phase III comparison of PCI to observation in locally advanced (Stage IIIA and IIIB) NSCLC patients

[36]. Of 356 patients accrued, 340 were eligible for analysis. Definitive treatment with either surgery or radiation, post-operative radiation, neoadjuvant, adjuvant, and concurrent chemotherapy were allowed on this trial. Patients were randomized to PCI, 30 Gy in 15 fractions or observation. Unfortunately, this study closed well short of its targeted accrual of 1058 patients which would have represented adequate power to demonstrate a 20% overall survival benefit.

The trial failed to demonstrate statistical significance regarding its primary end point of overall survival with a hazard ratio of 1.03 of death in the observation arm versus the PCI arm ($p = 0.86$) [36]. However, the rate of brain metastasis was 18.0% for the observation arm versus 7.7% in the PCI cohort with a p-value of 0.004; this represents a hazard ratio of 2.35 and an odds ratio of 2.52 [36]. The rate of grade 3 and 4 toxicities was very low, and most of these were acute in nature, and resolved; the authors reported only four patients with grade 3 or higher late toxicities. These randomized controlled trials of PCI for NSCLC are summarized briefly in **Table 2**.

• Toxicity, side effects & quality of life

In the setting of no demonstrable overall survival benefit from PCI for NSCLC, toxicity and side effects stemming from PCI have become the primary argument for forgoing this therapy in favor of observation. These negative effects with an accompanying reduction in the occurrence of brain metastases, however, must be weighed against the symptomatology that accompanies the emergence of overt symptomatic brain metastases when forgoing PCI.

Quality of life and neurocognitive assessments were reported from the recently completed RTOG trial, which utilized the HVLTL, the Activity of Daily Living Scale (ADLS), and the Mini-Mental Status Examination (MMSE) to track deterioration of neurocognitive functioning while also collecting data regarding

Table 2. Published randomized trials evaluating the role of prophylactic cranial irradiation in non-small-cell lung cancer.

Trial	Year of publication	Patients (n)	PCI dose (Gy/# of fractions)	Brain metastasis rate (%) (PCI vs no PCI)	p-value	Survival (PCI vs no PCI)	p-value	Ref.
VALG	1981	281	20/10	6 vs 13	0.038	Median 8.2 months vs 9.7 months	0.5	[32]
MDACC	1984	97	30/10	4 vs 27	0.02			[33]
RTOG 8403	1991	187	30/10	9 vs 19	0.10	Median 8.4 months vs 8.1 months	NS	[34]
SWOG	1998	254	37.5/15 or 30/10	1 vs 11	0.003	Median 8 months vs 11 months	0.004	[35]
RTOG 0214	2011	356	30/15	7.7 vs 18 (1 year rate)	0.004	75.6 vs 76.9 (1 year)	0.86	[36]

PCI: Prophylactic cranial irradiation.

patient-reported decline in cognitive function, fatigue, and global health/quality of life scores [37].

Quality of life was assessed utilizing the EORTC Quality of Life QLQ-C30 Questionnaire (QLQ-C30) and the BN20. Quality of life data were reported at 6 and 12 months, whereas MMSE and HVLTL results were reported at 3, 6 and 12 months [37]. There were no statistically significant differences in the QLQ-C30, the BN20, or patient-reported fatigue at either the 6 or 12 month time points [37]. There was a trend towards appreciable difference (unadjusted $p = 0.02$, $p = 0.24$) in patient-reported deterioration in cognitive functioning favoring the observation arm (18 vs 35%) at 6 months that became non-significant at 12 months. At 3 months, the MMSE showed 36% deterioration in the PCI group versus 21% in the observation patients ($p = 0.04$) [37]. This difference, again, failed to hold at the 6 and 12 month time points. Loss of independence based upon ADL testing failed to reach statistical significance between the two arms as well. HVLTL testing showed the greatest degree of deterioration in the PCI arm. At 3, 6 and 12 months, the HVLTL demonstrated statistically significant deterioration in recall in the PCI arm [37]. In both arms, there was a decrease in deterioration of recall at 12 months, compared with the 3 month score. The 1-year incidence of patients with deteriorated HVLTL scores was 26 versus 7% for the PCI versus observation cohorts, respectively (p -value of 0.03). A similar trend was noted in HVLTL delayed recall. Though not statistically significant at 6 months, this still showed deterioration in the PCI arm at 3 and 12 months. At 1 year, 32% of patients in the PCI group experienced HVLTL delayed recall deterioration compared with 5% in their observation counterparts. Of note in this study, the low accrual, far short of the intended power, significantly limited the ability to assess the role of newly developed brain metastasis in terms of possible diminution in neurocognitive and quality of life parameters. Additionally, the 1-year rate of brain metastasis was only 18% in this study. It should, therefore, be recognized that PCI does have risks associated with it, but in high risk populations, the risk of brain metastases and associated decline with growing intracranial lesions often outweighs the cognitive risk of PCI.

The suggestion of worsening memory following WBRT is not novel to this trial. DeAngelis *et al.* suggested that 1.9–5.1% of patients with

known brain metastasis treated with WBRT developed severe dementia; however, in their report, this effect was seen solely in patients treated with non-conventional brain radiation schedules and strategies, and in fact severe dementia was not seen in a single patient treated with a conventionally fractionated radiation course [38]. Other studies have focused upon the early effects of cranial irradiation, especially those occurring within the first few months, though the association of these phenomena with long-term effects have not been established [39–41].

When assessing cognitive changes, it is crucial to recognize the contribution and impact of several other variables, as indicated by Gondi *et al.* [42]. First, patients may have reduced neurocognitive ability prior to diagnosis or treatment which may or may not have been measured. Second, disease progression, intra-cranially or extra-cranially, may negatively influence neurocognitive as well as quality of life scores. Third, ameliorating medical interventions may cloud the picture or tamper with results. Fourth and finally, a lack in standardization of measurement tools makes cross-study comparison very challenging [42].

• Prognostic factors

The categorical conclusions thus far are that PCI decreases the incidence of brain metastases in patients with locoregionally advanced NSCLC, but this reduction comes with some deterioration in memory as measured by the HVLTL test. Therefore, in the future, it would be prudent to evaluate the role of PCI only in NSCLC patients at high risk for developing brain metastases, rather than the general population of all locoregionally advanced NSCLC patients. Several prognostic factors have been proposed as possible stratification variables for such an approach. These include histology, length of survival, age, and stage of disease [43].

Patients with adenocarcinoma have a higher rate of failure in the brain in some series [8]. Andre *et al.* showed, in a group including patients with cN2 disease, an almost three fold increase in isolated brain metastasis among those with adenocarcinoma versus those with squamous histology. The RTOG database also demonstrates a doubling of brain metastasis in adenocarcinoma versus non-adenocarcinoma, regardless of the use of chemotherapy [44].

As a patient lives longer, his or her risk of brain metastasis rises. Recursive partitioning analysis performed in over 1500 patients in the

RTOG database separated patients into four classes based upon multiple prognostic factors [45]. Despite longer lifespan, patients in Class I and Class II exhibited approximately twice the rate of brain metastasis, 18 versus 9% [45]. With improved therapies and multimodality approaches, patients with locally advanced disease have especially benefited from a survival standpoint, leaving them at higher risk of failure in common sites, such as the brain [46].

Age at diagnosis and stage of disease may also be important factors. A Canadian single institution retrospective review of 230 Stage IIIA and B patients receiving bi- or tri-modality therapy reported an overall brain metastasis rate of 34.2% by 2 years [47]. Among this group, age less than 60 was a statistically significant predictor of first failure in the brain with rates of 25.6 versus 11.4% for the less than versus greater than 60 years old groups. The underlying explanation for this phenomenon may be that older patients succumb to intercurrent disease earlier, and do not live long enough to develop brain metastases [47,48]. However, there may also be a difference in the biology of this disease as a function of age. Stage also alters the risk of developing brain metastasis. However, there is some debate as to whether nodal disease (N2) or extent of primary disease (T4) is more predictive of CNS involvement [48,49]. Also, neoadjuvant chemotherapy in trimodality approaches has been suggested to have a deleterious effect in increasing CNS involvement possibly by delaying definitive treatment of the primary disease [8].

Reparia *et al.* expanded upon these prognostic factors especially in the cohort of patients with adenocarcinoma [50]. Patients with brain metastases, in this retrospective study, had larger primary disease ($p = 0.006$) and were slightly older ($p = 0.044$) than those without. EGFR (25%) and KRAS (28%) were relatively common among patients with brain metastasis. Also, those with EGFR mutations and brain metastasis demonstrated a trend towards increased survival ($p = 0.067$) versus those with wild type or KRAS mutation disease [50].

• Current role of PCI in NSCLC

In spite of a clear reduction in the risk of developing brain metastases, PCI is currently not part of the standard of care for locally advanced NSCLC patients. In fact, although the absolute decrease may be less dramatic, the relative reduction in brain metastasis with PCI in NSCLC is on par with that of PCI in SCLC that showed a survival benefit in meta-analysis (Figure 1). Concerns continue regarding its long term toxicity especially late neurocognitive effects. The role of PCI should and likely will continue to be investigated, especially in better selected subsets of patients with greater risk of developing brain metastases. Some have suggested that, in such subgroups, instead of PCI, observation with frequent brain imaging in the post-treatment period would identify patients who proceed to develop brain metastases and these patients could be treated while still asymptomatic, as a consequence of 'earlier detection', and that such

Figure 1. Rate of brain metastasis in lung cancer with and without prophylactic cranial irradiation. Values approximated from Kaplan-Meier analyses of [18,34,36], weighted for sample size. NSCLC: Non-small-cell lung cancer; PCI: Prophylactic cranial irradiation; SCLC: Small-cell lung cancer.

an approach would improve outcomes, as the brain metastases would be treated ‘earlier’ [51]. However, with median survival close to four months after whole brain radiotherapy, irrespective of whether these are symptomatic or asymptomatic, it is unclear that such a strategy would be widely beneficial [52]. Instead, the hope has remained that a proactive approach utilizing PCI techniques with a reduced risk of cognitive deficits would at least decrease the rate of symptomatic brain metastases, and possibly improve survival in those with high risk NSCLC.

Innovations & future efforts

• Innovations in toxicity reduction

Of late, attention has shifted toward a reduction in WBRT-associated cognitive toxicities. Two primary interventions recently reported by the RTOG have generated considerable interest.

RTOG 0614 focused on the role of memantine as a pharmacologic intervention for mitigating the negative neurocognitive effects of WBRT for patients with brain metastases [53]. Memantine is a NMDA receptor antagonist that has been shown to be effective and well tolerated in vascular dementia patients [54]. All patients received WBRT and were randomized to either placebo or memantine at the start of radiotherapy; patients were treated for a total of 24 weeks. The WBRT schedule for this trial was 37.5 Gy in 15 fractions. The HVLt-R test (delayed recall) was utilized as the primary measure in RTOG 0614. Secondary testing included the MMSE, Trail Making Tests, Medical Outcomes Scale – Cognitive Function Scale, and the Functional Assessment of Cancer Therapy-Brain (FACT-BR) Quality of Life assessment.

Results were reported after 12.4 months median follow-up on 554 accrued patients, of whom 508 were deemed eligible [53]. Memantine was well tolerated and had a toxicity profile very similar to placebo. Although there was less decline in the primary endpoint of HVLt-R delayed recall at 24 weeks, this lacked statistical significance ($p = 0.059$) – possibly due to significant patient loss over time secondary to disease progression and death. However, this trial did demonstrate that memantine could slow cognitive decline (HR 0.78, $p = 0.01$) with a probability of cognitive function failure at 24 weeks of 53.8% in the memantine arm and 64.9% in the placebo arm. Superior results were also seen in the memantine arm for specific tests of executive function, processing speed, and memory [53].

RTOG 0933, on the other hand, represents an effort to lessen neurocognitive effects, by identifying ‘organs at risk’ (OAR) and utilizing conformal avoidance dose-delivery techniques (Figure 2) [55]. In this non-randomized Phase II trial, with a built-in historical comparator, prespecified end-points, and a-priori hypothesized endpoint improvements relative to the historic controls, intensity modulated radiation therapy (IMRT) was utilized to deliver hippocampal-avoidance whole brain radiation therapy (HA-WBRT). Of note, the OAR was not actually the anatomic hippocampus per se, but rather the dentate gyrus stem cell compartments involved in neurogenesis of cells responsible for a variety of memory functions such as processing, retention, and imprinting. These are known to be exquisitely radio-sensitive in preclinical models and associated with a radiation dose-clinical response effect relationship in clinical studies [42,56–57]. The primary outcome of RTOG 0933 was change

Figure 2. Example of hippocampal-avoidance whole brain radiation therapy.
Reproduced with permission from [59].

in HVLt delayed recall, with HVLt total recall, HVLt immediate recognition, FACT-BR quality of life assessment, Barthel's ADLs, overall survival, progression-free survival, and adverse events as secondary endpoints. These instruments have previously been deemed feasible and reproducible in brain metastases patients [58].

A total of 113 thirteen patients with brain metastasis, especially from NSCLC (56%) and breast (15%) cancer, were accrued, with 100 eligible for analysis [55]. The mean relative decline in HVLt delayed recall was 7% at 4 months with the historical control reaching 30%. This was a statistically significant result with a p-value of 0.0003. Total recall deterioration also compared favorably with prior historical series [60]. Interestingly, a trend towards statistical significance was observed for higher dose to 100% of the hippocampal dentate gyrus for a greater decline over time in HVLt delayed recall ($p = 0.084$) and HVLt immediate recognition ($p = 0.083$), suggesting a dose-response relationship. There was no demonstrated decline in FACT-BR quality of life scores nor in ADLs at 6 months from therapy. There was minimal toxicity associated with this therapy, though 3 patients (4.5%) progressed within the hippocampal avoidance region, a figure lower than the projected expectation [55].

Both of the approaches mentioned above need to be explored in the setting of PCI to alter the therapeutic ratio favorably, and this could result in broader application of PCI techniques to a variety of other tumors. It is especially important to note that the dose and fractionation, per current standards of care, differ between WBRT and PCI approaches. Because lower total doses and dose per fraction characterize PCI schedules, in comparison to WBRT schedules for treating brain metastases (for example, 25 Gy in ten fractions vs 30 Gy in ten fractions), one could speculate that the benefits seen with HA-WBRT might not readily be observed in the PCI setting; however, prior reports regarding the sensitivity of the hippocampus suggest that a D40% dose of >7.3 Gy, converted to equivalent dose in 2-Gy fractions, assuming an α/β ratio of 2.0, has been validated in a prospective trial as being significantly associated with cognitive decline; this dose would universally be delivered to the bilateral hippocampi, even with the lower doses and dose per fraction used in PCI regimens [57]. Two pending RTOG studies represent efforts

to further test these tactics. One will randomize SCLC patients to standard PCI versus PCI with hippocampal-avoidance to a total dose of 25 Gy in ten fractions. The other is a randomized trial in patients with brain metastases to test the possible additive value of both memantine and HA-WBRT.

• Future efforts in other malignancies

With the possibility of multiple improvements on the horizon for PCI, there remains the legitimate question of whether the role for PCI could be expanded into other primary malignancies. Considering the prevalence of various malignancies and their respective proclivities for CNS metastasis, a logical next foray may be in breast cancer and melanoma.

It has previously been established that breast cancer may also be risk-stratified for brain metastasis based upon certain prognostic factors [61]. Among these is HER-2-overexpression, which has been shown to increase the risk of brain metastasis by over fourfold [61]. Bendell *et al.* retrospectively reviewed 122 patients treated with trastuzumab alone or with combined chemotherapy for HER-2 overexpressing breast cancer [62]. In this series, 34% of patients had brain metastases. Noted by the authors was the strikingly common occurrence of stable extracranial disease associated with brain metastasis and intracranial progression – likely secondary to trastuzumab's poor penetration through the blood–brain barrier. A large Canadian tissue archival study further confirmed the predilection for brain metastasis in HER-2 positive breast cancer [63]. With a median follow-up of 14.8 years, 3726 patients' pathologic specimens were examined and compared with outcomes. HER-2 enriched and basal-like subtypes showed 28.7 and 25.2% brain metastasis rate, a rate much higher than other subtypes.

This represents only one of many prognostic factors that may allow for selection of patients who would most likely benefit from PCI. Hicks *et al.* utilized tissue microarrays to compare breast cancer patients with brain metastases to counterparts either without metastasis or with extracranial metastasis [64]. Age less than 50 years, ER negativity, HER-2 positivity, high grade, cytokeratin 5/6 expression, and EGFR expression were all predictive for brain metastasis. Very limited retrospective data are available, regarding the role of PCI in breast cancer, and these have been disappointing, overall [65].

As PCI techniques improve, the possibility of an improved therapeutic window suggests that these could be likely patient subsets for testing the value of PCI.

Conclusion

PCI has shown great efficacy in reducing the rates of brain metastasis in leukemia, SCLC and NSCLC. Additionally it has shown an overall survival benefit in a well-selected group of SCLC patients. Among subsets of both limited stage and extensive stage patients, PCI has become the standard of care.

In NSCLC, PCI has yet to reach an acceptable risk-benefit ratio so as to enter mainstream clinical use. Continued research is necessary not only to accrue studies of sufficient power to demonstrate a survival benefit, but also to further elucidate the prognostic factors that may portend a higher risk for brain metastasis. Similar efforts could be considered in other malignancies in order to clarify the role of PCI and target its use to these high risk subsets.

The toxicities from PCI remain a matter of considerable focus. There are clearly deleterious effects which center around neurocognitive function and memory. With advances in technology and medical management, the negative effects of PCI may be further limited or mitigated. PCI continues to be investigated actively as to its roles in multiple malignancies. Continued research

is necessary to define its usefulness outside of leukemia and SCLC.

Future perspective

The role of PCI in NSCLC as well as in other malignancies will be of particular interest in coming years. In particular, the effect of improved medical management and WBRT techniques upon the risk-benefit ratio associated with PCI will be integral in clarifying its usefulness in highly selected patients with disease other than SCLC.

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References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- Nesbit ME, Sather H, Robison LL *et al.* Sanctuary therapy: a randomized trial of 724 children with previously untreated acute lymphoblastic leukemia: a report from Children's Cancer Study Group. *Cancer Res.*42, 674–680 (1982).
- Hansen HH. Should initial treatment of small cell carcinoma include systemic chemotherapy and brain irradiation? *Cancer Chemother. Rep.*34, 239–241 (1973).
- Hochstenbag MM, Twijnstra A, Wilmink JT *et al.* Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. *J. Neurooncol.*48, 243–248 (2000).
- Gaspar L, Scott C, Rotman M *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int. J. Radiat. Oncol. Biol. Phys.*37, 745–751 (1997).
- Komaki R, Cox JD, Whitson W. Risk of brain metastases from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. *Cancer Treat. Rep.*65, 811–814 (1981).
- Hirsch FR, Paulson OB, Hansen HH *et al.* Intracranial metastases in small cell carcinoma of the lung: correlation of clinical and autopsy findings. *Cancer*50, 2433–2437 (1982).
- Albain KS, Rusch VW, Crowley JJ *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group Phase II study 8805. *J. Clin. Oncol.*13, 1880–1892 (1995).
- Andre F, Grunenwald D, Pujol JL *et al.* Patterns of relapse of N2 non-small cell lung carcinoma patients treated with preoperative chemotherapy. *Cancer*91, 2394–2400 (2001).
- Gaspar LE, Chansky K, Albain KS *et al.* Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J. Clin. Oncol.*23, 2955–2961 (2005).
- Arriagada R, LeChevalier T, Borie F *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J. Natl Cancer Inst.*87, 183–190 (1995).
- Kristjansen PE, Kristensen CA. The role of prophylactic cranial irradiation in the management of small cell lung cancer. *Cancer Treat. Rev.*19, 3–16 (1993).
- Rosen ST, Makuch RW, Lichter AS *et al.* Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer: potential benefit restricted to patients with complete response. *Am. J. Med.*74, 615–624 (1983).
- Aroney RS, Aisner J, Wesley MN *et al.* Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat. Rep.*67, 675–682 (1983).
- Ohonoshi T, Ueoka H, Kawahara S *et al.* Comparative study of prophylactic cranial

- irradiation in patients with small cell lung cancer achieving a complete response: a long-term follow-up result. *Lung Cancer*10, 47–54 (1993).
- 15 Wagner H, Kim K, Turrisi A *et al.* A randomized Phase III study of prophylactic cranial irradiation vs observation in patients with small cell lung cancer achieving a complete response: final report of an incomplete trial by the ECOG and RTOG. *Proc. Am. Soc. Clin. Oncol.*15, 376 (1996).
 - 16 Gregor A, Cull A, Stephens RJ *et al.* Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicenter randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur. J. Cancer*33, 1752–1758 (1997).
 - 17 Laplanche A, Monnet I, Santos-Miranda JA *et al.* Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *Lung Cancer*21, 192–201 (1998).
 - 18 Auperin A, Arriagada R, Pignon JP *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N. Engl. J. Med.*341, 476–484 (1999).
 - **Practice-altering meta-analysis demonstrating overall survival benefit to prophylactic cranial irradiation (PCI) in small-cell lung cancer (SCLC).**
 - 19 Patel S, Macdonald OK, Suntharalingam M. Evaluation of the use of prophylactic cranial irradiation in small cell lung cancer. *Cancer*115, 842–850 (2009).
 - 20 Meert AP, Paesmans M, Berghmans T *et al.* Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*1, 5 (2001).
 - 21 Komaki R, Meyers CA, Shin DM *et al.* Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. *Int. J. Radiat. Oncol. Biol. Phys.*33, 179–182 (1995).
 - 22 Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. *Semin. Oncol.*31, 702–713 (2004).
 - 23 Wolfson AH, Bae K, Komaki R *et al.* Primary analysis of a Phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.*81, 77–84 (2011).
 - 24 Le Pêchoux C, Dunant A, Senan S *et al.* Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99–01, EORTC 22003–08004, RTOG 0212, and IFCT 99–01): a randomised clinical trial. *Lancet Oncol.*10, 467–474 (2009).
 - 25 Gondi V, Paulus R, Bruner DW *et al.* Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int. J. Radiat. Oncol. Biol. Phys.*86, 656–664 (2013).
 - 26 Lee J, Bekele B, Zhou X *et al.* Decision analysis for prophylactic cranial irradiation for patients with small-cell lung cancer. *J. Clin. Oncol.*24, 3597–3603 (2006).
 - 27 Govindan R, Page N, Morgensztern D *et al.* Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J. Clin. Oncol.*24, 4539–4544 (2006).
 - 28 Slotman B, Faivre-Finn C, Kramer G *et al.* Prophylactic cranial irradiation in extensive small-cell lung cancer. *N. Engl. J. Med.*357, 664–672 (2007).
 - 29 National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer Version 2. www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (2014).
 - 30 Schild SE, Foster NR, Meyers JP *et al.* Prophylactic cranial irradiation in small-cell lung cancer: findings from a North Central Cancer Treatment Group Pooled Analysis. *Ann. Oncol.*23, 2919–2924 (2012).
 - 31 Mamon HJ, Yeap BY, Janne PA *et al.* High risk of brain metastases in surgically staged IIIA non-small cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J. Clin. Oncol.*23, 1530–1537 (2005).
 - 32 Cox JD, Stanley K, Petrovich Z *et al.* Cranial irradiation in cancer of the lung of all cell types. *JAMA*245, 469–172 (1981).
 - 33 Umsawasdi T, Valdivieso M, Chen TT *et al.* Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J. Neurooncol.*2, 253–259 (1984).
 - 34 Russell AH, Pajak TE, Selim HM *et al.* Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int. J. Radiat. Oncol. Biol. Phys.*21, 637–643 (1991).
 - 35 Miller TP, Crowley JJ, Mira J *et al.* A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer. *Cancer Ther.*4, 229–236 (1998).
 - 36 Gore EM, Bae K, Wong SJ *et al.* Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J. Clin. Oncol.*29, 272–278 (2011).
 - **Most recent analysis of the role of PCI in non-small-cell lung cancer (NSCLC).**
 - 37 Sun A, Bae K, Gore EM *et al.* Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J. Clin. Oncol.*29, 279–286 (2011).
 - **Quality of life analysis associated with RTOG 0214.**
 - 38 DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology*39, 789–796 (1989).
 - 39 Welzel G, Fleckenstein K, Schaefer J *et al.* Memory function before and after whole brain radiotherapy in patients with and without brain metastases. *Int. J. Radiat. Oncol. Biol. Phys.*72, 1311–1318 (2008).
 - 40 Chang EL, Wefel JS, Hess KR *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.*10, 1037–1044 (2009).
 - 41 Li J, Bentzen SM, Renschler M *et al.* Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J. Clin. Oncol.*25, 1260–1266 (2007).
 - 42 Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol.*97, 370–376 (2010).
 - 43 Frezza G, Salvi F. Prophylactic cranial irradiation in non-small cell lung cancer. *Ann Oncol.*17(Suppl. 2), ii76–78 (2006).
 - 44 Cox JD, Scott CB, Byhardt RW *et al.* Addition of chemotherapy to radiotherapy alters failure patterns by cell type within

- non-small cell carcinoma of the lung. *Int. J. Radiat. Oncol. Biol. Phys.*43, 505–509 (1999).
- 45 Komaki R, Scott CB, Byhardt R *et al.* Failure patterns by prognostic group determined by recursive partitioning analysis (RPA) of 1547 patients on four radiation therapy oncology group (RTOG) studies in inoperable non-small-cell lung cancer (NSCLC). *Int. J. Radiat. Oncol. Biol. Phys.*42, 263–267 (1998).
- 46 NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet*375, 1267–1277 (2010).
- 47 Carolan H, Sun AY, Bezjak A *et al.* Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer*49, 109–114 (2005).
- 48 Ceresoli GL, Reni M, Chiesa G *et al.* Brain metastases in locally advanced non-small cell lung carcinoma after multimodality treatment risk factor analysis. *Cancer*95, 605–612 (2002).
- 49 Bajard A, Westeel V, Dubiez P *et al.* Multivariate analysis of factors predictive of brain metastases in localized non-small cell lung carcinoma. *Lung Cancer*45, 317–323 (2004).
- 50 Raparia K, Villa C, Mehta MP, Cagle P. Clinical, pathological and molecular predictive factors for the development of brain metastasis in patients with lung adenocarcinoma [abstract]. 93(Suppl. 1), 464A (2013).
- 51 Yokoi K, Kamiya N, Matsuguma H *et al.* Detection of brain metastases in potentially operable non-small cell lung cancer. A comparison of CT and MRI. *Chest*115, 714–719 (1997).
- 52 Kepka L, Cieslak E, Bujko K *et al.* Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: the RTOG RPA intra-classes analysis. *Acta Oncol.*44, 389–398 (2005).
- 53 Brown PD, Pugh S, Laack NN *et al.* Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.*15, 1429–1437 (2013).
- **Medical management may improve the risk-benefit ratio of PCI.**
- 54 Orgogozo JM, Rigaud AS, Stöfler A *et al.* Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke*33, 1834–1839 (2002).
- 55 Gondi V, Mehta MP, Pugh SL *et al.* Memory preservation with conformal avoidance of the hippocampus during whole-brain radiotherapy for patients with brain metastases: primary endpoint results of RTOG 0933. Presented at: *American Society for Radiation Oncology 2013 Annual Meeting*, Atlanta, GA, USA, 22–25 September 2013.
- **Hippocampal-avoidance whole brain radiation therapy may significantly improve the risk-benefit ratio of PCI.**
- 56 Monje ML, Mizumatsu S, Fike JR *et al.* Irradiation induces neural precursor-cell dysfunction. *Nat. Med.*8, 955–962 (2002).
- 57 Gondi V, Hermann BP, Mehta MP, Tome WA. Hippocampal dosimetry predicts neurocognitive function impairment following fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int. J. Radiat. Oncol. Biol. Phys.*83, 487–493 (2011).
- 58 Regine WF, Schmitt FA, Scott CB *et al.* Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of radiation therapy oncology group trial BR-0018. *Int. J. Radiat. Oncol. Biol. Phys.*58, 1346–1352 (2004).
- 59 Gondi V, Tolakanahalli R, Mehta MP *et al.* Hippocampal-sparing whole-brain radiotherapy: a ‘how-to’ technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*78(4), 1244–1252 (2010).
- 60 Chang EL, Wefel JS, Hess KR *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.*10, 1037–1044 (2009).
- 61 Gabos Z, Sinha R, Hanson J *et al.* Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. *J. Clin. Oncol.*24, 5658–5663 (2006).
- 62 Bendell JC, Domchek SM, Burstein HJ *et al.* Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*97, 2972–2977 (2003).
- 63 Kennecke H, Yerushalmi R, Woods R *et al.* Metastatic behavior of breast cancer subtypes. *J. Clin. Oncol.*28, 3271–3277 (2010).
- 64 Hicks DG, Short SM, Prescott NL *et al.* Breast cancers with brain metastases are more likely to be estrogen receptor negative, express the basal cytokeratin CK5/6, and overexpress HER2 or EGFR. *Am. J. Surg. Pathol.*30, 1097–1104 (2006).
- 65 Huang F, Alrefae M, Langleben A *et al.* Prophylactic cranial irradiation in advanced breast cancer: a case for caution. *Int. J. Radiat. Oncol. Biol. Phys.*73, 752–758 (2009).
- **Future avenues may exist for PCI in other malignancies outside of lung cancer and leukemia.**