This past summer’s meta-analysis and this issue’s review article would seem to ice the cake for making prophylactic cranial irradiation (PCI) for patients with small cell lung cancer a no-brainer. The long-awaited proof of a survival advantage is now in hand [1]. Seemingly this should silence those that decried PCI as unnecessary and even dangerous. Perhaps if all who were treated stood such a substantial chance of being injured by PCI, even a survival gain would be considered counter-productive because of the toxicity. Recently, I dined with a lung cancer expert whom I hold in high regard. He waxed prophetic that he would refuse this treatment for himself, and would not recommend it to a relative. Even the respected leaders are not always enlightened by the emerging facts.

I guess it is hard to bury a legend no matter how weak the data bolstering it. It’s hard to accept a banished warrior even when the indictment has been dismissed and the jury not only finds for acquittal but even finds him a hero rather than a perpetrator. This is especially true when usually sober opinion leaders have been immoderate in their premature damning of what ultimately turns out to be a valuable tactic.

Are there continuing credible facts about the neurocognitive risk of PCI? The case reports and series summaries calling attention to the risks of PCI are all aged and weakened by faulty methodology. Yang and Matthews [2] in the current review and analysis include some of these, and the labored analysis by Suwinski et al. [3] includes all of the studies in an attempt to define a dose-response and timing relationship with PCI. The problems with these data studies are legion: crude versus actuarial survivals; lack of cumulative frequency of relapse; short survival leading to many patients dying with poor systemic or local control before they metastasize to the brain, and retrospective data with lack of uniform screening for the relapse of the brain event. My largest irritation with these reports is the extraordinary reporting bias: problems with long-term survivor neurocognitive dysfunction fall on PCI, but no one tallies the dysfunction caused by brain metastasis in those not receiving PCI. Today we know that many patients present with neurocognitive dysfunction before any systemic, local or brain treatment is applied [4]. In the reports from the 1970s and 1980s, patients received months and months of post-PCI chemotherapy with the likes of lomustine, procarbazine, doxorubicin, vincristine, methotrexate, and alkylators—many cross damaged blood-brain barriers and perhaps all chemotherapy drugs after PCI have been applied. Sometimes the systemic therapy lasted as long as two years! Median survivals and two-year survivals for limited-staged patients treated in this era were half what it is today, so the long-term surviving population was less than today.

In North America and Japan, the 1990s brought an era of cisplatin and etoposide as systemic therapy and a shortened duration of systemic therapy to only four to six cycles. Those physicians who continued, despite adverse publicity, to use PCI, did so after completion of systemic therapy. If the idea was that the central nervous system was the only site where chemotherapy was barred, why would one use PCI if viable or resistant systemic disease persisted and required further chemotherapy? Sensibly one would clean up systemic and
local disease with intensive and early therapy, then “play the PCI card” to complete therapy. Sawinski and colleagues [3] argue from a theoretic vantage—rapidly re-populating tumors double and require larger doses, so earlier treatment must be better and one must pay a price for a delay. The assumptions underscore their analysis, which also accepts that each of the case reports accurately identifies brain relapses. It lumps large and small series and case reports together to support their hypothesis. The theory is weakly supported by very wizened data with too many variables besides timing, and if two to four small studies are eliminated, the strength of their case vanishes. But rather than argue “early is better” away, let’s have a prospective trial to test this hypothesis.

Since the policy of “wait until complete response and completion of chemotherapy” has been practiced, reports of major durable neurotoxicity have virtually disappeared. Perhaps the switch to four cycles of cisplatin and etoposide is the real story of the decline in neurotoxicity attributed to PCI. Yet the long shadow of personal memorable cases of bad outcomes, trumpeting from opinion leaders, and an unwillingness to deal with present-day facts lead to the continued bias about the risk of PCI causing neurotoxicity.

Facts from the pre-cisplatin/etoposide era suggested that the brain relapse rate was only about 20%, and it was reduced to 5% with PCI. With patients living longer, the prospective trials from France [5, 6] and the United Kingdom [7] discussed in the review by Yang and Matthews [2] correct our myopic view—the rate of initial relapse in the brain is 50% to 60% without PCI! The magnitude of the risk is much larger than initially thought. Observation leads to brain relapse, and brain relapse surely is associated with neurologic dysfunction as well as unmeasured neurocognitive deficits and ultimately death. Is it better to warn your patient about the risk of giving PCI or the risk of avoiding it? Which is worse?

Are these newer studies showing high rates of neurocognitive deficits? In fact, the newer studies are faulted and faulty because they do not provide long enough follow-up with repeat studies to give the absolute confidence that there is no difference between observation groups and treated groups. However, the facts that we have from these recent studies do not point to a large frequency of durable cognitive defects. One of the conundrums is that the group that fails with brain metastasis is no longer suitable for these complex tests. There is some evidence that there are neurocognitive defects in patients at diagnosis before any systemic or cranial treatment [4]. Aihes [8] has reported transient deficits in mental examinations when one compares patients from just before treatment to just after treatment. Unfortunately, there is no long-term follow-up from this relatively small series to see if these measured problems endured or all went away. The Arrigada study [5] reported no significant difference in neurocognitive deficits for patients treated with PCI or those observed. The frequency of these abnormalities was in the range of 10% or less. However, few repeat neurocognitive studies were done beyond three years. By contrast, none of the 60% from the series that suffered brain metastasis were able to complete follow-up studies because they went on to die of their small cell cancer mostly within a few months of diagnosing brain mets. The British series [7] reports transient deficits that seem to reverse with follow-up.

The review [2] in this issue of The Oncologist again mentions the issue of fraction size. Many U.S. radiation oncologists eschew larger dose per fraction PCI because it is “suboptimal” and large fraction sizes lead to more “late-effect” damage. No doubt, theory and radiobiological dogma indict large doses per fraction. However, in the meta-analysis studies [1], the most commonly used schedules showing survival advantages employed 3 Gy! Theoretically, larger doses per fraction can cause a higher risk of later effects (if a tolerance dose is achieved), and neural tissue is theoretically the most sensitive to these type of effects. However, if fraction size were the critical factor, the French and British trials should report obvious injury even with three years of follow-up. But there is silence on this point from Europe. While there is reason to have some concern for larger fraction sizes, there is more reason to accept the best data in hand, which have used 3 Gy fractions. At least at this time, there is no reported difference in neurocognitive deficits with these regimens when compared to observation without PCI.

Surveillance scans with CTs or MRIs are expensive and do not work well. Hardy [9] published on this policy in the early 1990s and found that more metastases occurred between the interval scans, and more importantly that therapeutic radiation was unsuccessful at palliating symptoms and restoring lost performance status after overt metastases spread. The French trial [5] reported frequent abnormalities on images, but the abnormalities lacked any clinical correlation. So why perform costly procedures that do not improve quality of life or survival instead of irradiation, which will be needed in more than the majority of patients anyway?

The issues for PCI are not whether to use it or not. It is factually clear that it does what it intends to do—reduces brain relapse and improves survival. But does it lower brain relapse to acceptable rates? Optimal would be a relapse rate of zero with no neurocognitive deficits. This requires trials of higher doses versus lower doses, different fraction schemes and different timing. Is fraction size a critical variable here? If neurocognitive deficits are an issue related to fraction size, a hyperfractonated dose (1.2 Gy twice daily) predicts the lowest risk—no one as yet has published on this type of schedule for small-cell PCI. A schedule of 1.5 BID to 36 Gy, an accelerated scheme, has been piloted (Aaron Wolfson, University of
Europeans have joined together to mount a trial comparing two variations of low dose 24-25 Gy to two variations of high dose 36 Gy (in two different methods) (Cecile Le Pechoux, Institute Gustave Roussy, personal communication). Few U.S. centers have joined this trial, and neither the cooperative groups nor the National Cancer Institute have been very enthusiastic about joining it.

The data mandate PCI use—higher doses seem to reduce relapse rates. If the survival advantage is not sufficiently convincing, and reduction in relapse in the brain is only minimal, then many will continue to experience brain relapse. Best practice and evidence points us toward using PCI for all complete responders. If one continues to fear the reports and shadows of the past, use low dose per fraction to some reasonable dose (however, the British trial suggests that 24 Gy in twelve 2 Gy fractions is no better than observation). While 25 Gy in 10 fractions has been used safely in the last 15-20 years, larger total doses even in relatively large doses per fraction seem very reasonable. Trials would be better, but the preponderance of evidence points in this direction. In the last decade, evidence that PCI is harmful after cisplatin/etoposide and thoracic radiotherapy is remarkably thin. If done earlier with new drugs or chemotherapy after the PCI, regardless of fraction size, we have fewer facts and no evidence.

What seems a no-brainer to me is that an actual failure rate is in excess of 50% in the brain after observation and avoidance of PCI, and this causes more central nervous system dysfunction than PCI at any dose. Is it the shadow of past personal experiences or case reports that keep us from recognizing this?

ACKNOWLEDGMENT
I thank Dr. Eli Glatstein for reading my remarks and Nancy Miller for preparing them.

REFERENCES


