


M19-02
Bi-modality vs. Trimodality in Stage III NSCLC, Thur, Sept 6, 10:30 - 12:00
Bi-modality versus tri-modality therapy in stage IIIa NSCLC: Where does the data lead us?
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Improving survival outcomes for patients presenting with mediastinal lymph nodes, Stage IIIA, N-2, motivates thoracic surgeons, medical oncologists and radiation oncologists alike. All desire the best treatment for the most patients, but we continue to debate what current tactics are most likely to result model that we can readily adopt. With an eye to the future, most hope that a gene array or molecular identifier will forecast which patients have tumors with genetic packages that are amenable to curative therapy. Alas, we are not to that point today, and the 30% of NSCLC patients with heterogeneous stage IIIa disease variously are treated with the best of intentions based on a rather weak foundation of clinical trials. All stage IIIa is not the same, and a one-size fits all, bi- or tri-modal therapy is likely to be error-prone and unsatisfactory to us all. What is abundantly clear is that no single modality alone is appropriate, and the wish for surgery to be the most successful tactic leads us into the temptation to use it more widely than appropriate for the extant data. The same can be said for radiotherapy alone, which is clearly inferior to radiotherapy plus chemotherapy in patients that can tolerate chemotherapy. Unlike the stringent winnowing process selecting patients for surgery, radiotherapy discriminates less and can more easily be applied to the entire population presenting with lung cancer. Poor heart and lung functions are not the same barrier for radiotherapy as these are for surgery. The presence of N-2 nodes indicates that the deanged tumor cell-line has metastatic potential beyond the thorax, more likely than not. Thus, it is quite clear that the use of chemotherapy in N-2 patients is desirable on theoretic grounds (they metastasize) and clinical data (survival) is better, but we must remember that the studies done supporting that always mandate that the patients have good performance status and can withstand systemic therapy. Cisplatin is the most universally accepted drug, but pairing it with another agent has not resulted in a combination that everyone is willing to use. Europeans have recognized this and allowed investigator physicians to choose what other drug to add to cisplatin.

The landmark CALGB study initiated in 1984 established that this platinum-based chemotherapy added to radiotherapy was better than radiotherapy alone (Dillman). Over the ensuing two decades, there have been nationalistic tendencies to use certain chemotherapy pairs with cisplatin, or even carboplatinum, but no pair of drugs emerges as superior, and three drugs seems to increase toxicity without adding a survival gain. The international standard of care for stage IIIa patients remains chemoradiotherapy, but the drugs, the timing of the two modalities (concurrent or sequential) and the penetrating question of whether a select subset might benefit from more remains unanswered. Underpowered phase III and highly publicized phase II studies have tried to establish chemotheraphy for two or three cycles followed by surgery. Even for N-0 patients and for N-2 patients, the complete response is in the single digits, or if reported higher, the confidence interval includes less than 10% (Pisters et al). Many have clamored for the newer chemotheraphy agents introduced in the 1990’s, particularly carboplatinum paclitaxel in the US, and while these are used, none of these have actually added substantially to the cisplatin plus a “V” drug combination.

Tri-modal therapy began with the SWOG trial 8805 (Albain et al). This trial’s 120 plus patients provided the data that formed the basis and the hypothesis for the US Intergroup 0139 trial. The backbone of both trials is cisplatin etoposide and concurrent radiotherapy, 45 Gy preoperative-ly, or 61 Gy definitively in the non-surgical arm of the Intergroup trial. Those that had induction chemoradiotherapy had a 10 - 30% chance of complete pathologic response in N-2 nodes, and these patients had long term prospect of survival, whereas those with residual disease in nodes almost universally failed. Moreover, supplementary post operative therapy (post operative boost radiotherapy or adjuvant chemotherapy) only increased morbidity and did nothing to salvage these less than complete nodal responders.

The major trials addressing the addition of surgery remain inconclusive. The largest and purest is the US Intergroup 0139, where patients were randomized to chemoradiotherapy to full radiotherapy dose of 61 Gy or truncating the dose to 45 Gy when used pre-operatively, both concurrent with cisplatin etoposide chemotherapy (Albain 2). Despite a significant benefit in disease free survival, there was no significant benefit in overall survival. Subset analyses show a hazard to pneumonectomy, particularly right sided, and a potential for benefit in patients requiring lobectomies. The negative impact of right pneumonectomies on overall survival has been pinned on the tri-modal therapy implicating the radiotherapy. Martin et al first called attention to the identical 25% mortality from a Memorial series that used chemotherapy alone, and indeed many sources note increased mortality with the pneumonectomy by itself without any adjuvant therapy. Andrez forecast from over 700 French patients with N-2 NSCLC that four factors were key: single station, single lymph nodes, clinically obvious nodes by imaging did worse than incidental nodes, and using neoadjuvant chemotherapy. VanMeerbeck and the EORTC recently reported a trial using 2 to 3 induction cycles of chemotherapy based on a platinum plus one other modern drug. Nearly half of the 579 patients registered were randomized to resection or radiotherapy, but 47% of patients did not proceed after induction therapy for a variety of reasons. Despite eliminating some of the most unfavorable cases during the induction treatment, there was no difference in median or five year survival. The US Intergroup has not been closed a minimum of 6 years, but at last report, surgery achieved 27% and chemoradiotherapy 20% 5 year survival (NS). The EORTC trial reported 16% versus 17% 5 year survival (NS) for patients randomized to surgery and radiotherapy respectively. Undoubtedly there were differences in selection and other factors between these studies, but the EORTC study had the more modern chemotherapy, and the US Intergroup study was less successful in administering the post
operative chemotherapy in patients subjected to surgery, and the radiotherapy treatment plan compliance was faulty in 20% of cases. Some believe that chemotherapy can achieve better results when used alone, and that radiotherapy adds nothing but morbidity. While this ultimately may prove correct, the current data suggest that nodal response is less, and that morbidity seems to be more associated with pneumonectomy than radiotherapy use. Those advocating radiotherapy underscore the enhanced complete response rate, and the possibility of eliminating clones of chemotherapy resistant cells. The US has mounted a trial comparing induction docetaxel platinum alone to docetaxel platinum plus radiotherapy prior to resection. It is accruing very slowly. Intrinsic factors such as number of nodes, number of nodal levels positive for cancer, and bulk - all hard to define pre-operative - may be telling, and how these factors are allocated may influence the results of randomized trials more than the treatment itself.

The standard bi-modal management is chemoradiotherapy. This should be the control arm of any trial testing the value of surgery, which seems very attractive, but remains of unproven value in stage IIIa disease.


Session M20: Patients - Health Care Provider Communication

M20-01 Patients - Health Care Provider Communication, Thur, Sept 6, 10:30 - 12:00

The cost of care for patients with lung cancer

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The worldwide epidemic of lung cancer is a major public health concern, not only because of the enormous loss of life and the great morbidity it causes, but also because of the large economic burden it places on health care systems and society in general. Based largely on 1990 data sources, the economic burden of cancer in general has been estimated in the United States at US$ 27.5 billion for direct health care costs including hospitalized care costs of $17.9 billion. Indirect costs have been estimated at a further $58.7 billion. As a percentage of the total health care expenditures in the United States, cancer constitutes about 4.7% of all costs.

Based on expenditure data from the 1996 Surveillance, Epidemiology and End Results (SEER) database, Brown et al. estimated the direct medical care costs to be $4.7 billion for lung cancer (1). A cost per case study from California in 1997 estimated the long-term costs of care for lung cancer to be $33,000 compared with $35,000 for breast and $42,000 for colon (2).

The total cost burden of lung cancer will be high in industrial countries where the high incidence of lung cancer and adequate resources enable state-of-the-art care to be given. This economic burden may exceed the capacity of developing countries to provide appropriate evidence-based care. Even wealthy nations are experiencing increasing fiscal constraint which is forcing governments and health care administrators to critically examine the value of health care interventions and the efficiency of health care delivery systems.

Health economic data may be presented in many forms - as the cost to treat an individual (cost per case), as the economic impact to the funder (government in a publicly funded system; an insurer in a private coverage system) of the total number of treated cases over a defined period, or as the costs in relation to the consequences in comparison to alternative interventions. The latter is increasingly expected by governments prior to approval as it provides an estimate of the value of the intervention against the money expended.

A cost-effectiveness analysis is the most common of these analyses and provides information on the incremental cost of the intervention compared to the standard therapy over the incremental benefit measured in life years gained. The incremental cost per case (ICER) can then be used by decision makers to determine if a new therapy represents good value for money or is cost-effective. A value less than $50,000 per life year gained (LYG) is generally accepted as “cost-effective” but there is little to recommend this specific number. A range is more acceptable and may be of the magnitude of $20,000-100,000/LYG. The weakness of the cost effectiveness analysis is that it does not take account of the morbidity of the disease state and its treatment. A quality adjusted life year (QALY) incorporates morbidity into a single multi-dimensional measure (i.e. the quantity of life gained by treatment is weighted by the quality of that life). The quality of life is approximated by a utility which is a measure of preference for a given health state rated on a scale where 0 equals death and 1 equals perfect health. “Standard gamble” exercises, time trade off and direct rating on a visual analogue scale can be used, as well as specific instruments such as the Health Utilities Index and Euro Qol.

Economic evaluations are relatively specific to the health care system they are performed in and cannot readily be used for decision-making in another health care system with a different delivery system, patterns of practice and cost structure. In interpreting the results of an economic analysis, it is important to be aware of issues such as transparency, the use of discounting and sensitivity analysis and the methodologies for assessing effectiveness. The interested reader is directed to guidelines for reporting economic studies (3) and strategies to critically appraise economic analyses (4,5).

Early studies of Canadian lung cancer costs revealed some surprises and also helped to guide efforts to use resources more effectively. Studies from the National Cancer Institute of Canada (6,7) demonstrated that the use of chemotherapy in advanced NSCLC could actually be a dominant strategy, (i.e. it prolonged survival while reducing costs), as it led to the use of fewer radiation and late stage hospital resources.