Solunum 3, Özel Sayı 2:215-216, 2001

THE RATIONALE AND RESULT OF INDUCTION THERAPY PRIOR TO SURGICAL RESECTION IN THE MANAGEMENT OF LOCALLY ADVANCED AND EARLY STAGE LUNG CANCER

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There have been many retrospective reports in the recent literature suggesting that patients with N2 disease can be cured if surgical resection is complete. Most of the patients cured initially presented with clinical stage I or II disease. Incomplete resections, with residual gross or microscopic disease rarely lead to 5 year survival. Selectivity is the important factor in deciding whether or not to offer primary surgery to patients with preoperatively identifiable N2 disease. Multiple lymph node sites, bulky extra-capsular disease, T3 tumors and non-squamous cell histology all adversely affect prognosis. Recent phase III randomized trials suggest that primary surgery in preoperatively identified N2 disease (mediastinoscopy) is futile.

In the most favorable cases where N2 disease has been discovered serendipitously at the time of surgery, a 30% 5 year survival rate can be expected when complete surgical excision including mediastinal lymph node dissection has been performed.

More bulky N2 disease is considered by most surgeons to be inoperable, most patients being offered radiotherapy as definitive treatment. Preoperative radiotherapy followed by surgical resection has offered no benefit. There has been a recent flurry of activity examining the role of induction treatment combined with surgical excision for this nore advanced type of N2 disease. Many phase II trials have been reported. Three phase III trials comparing surgical treatment to induction chemotherapy followed by surgery have shown a decided benefit for the latter approach. Similarly, chemoradiotherapy as a primary treatment has been shown to be more beneficial than radiotherapy alone and may be as effective as a surgery approach. Presently, a North American trial is halfway through accrual comparing induction therapy followed by surgery with standard radiotherapy approaches without surgery.

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CURRENT STATUS OF MULTIMODALITY THERAPY

The results of surgical trials which include induction chemotherapy or chemoradiotherapy have demonstrated the following: 1) Bi or trimodality therapy is better than surgery alone in treating locally advanced lung cancer, 2) patients who respond either completely or partially to this induction therapy and are down-staged have a better survival, 3) those patients who have persisting N2 disease at the time of surgery have a much more disappointing five year survival and 4) incompletely resected patients are rarely cured of their disease. These induction therapies are tolerable without apparent undue morbidity either during the induction phase or the postoperative phase of treatment. However, there is concern that morbidity and mortality increases if a right pneumonectomy has to be performed. Surprisingly, in the reported phase III trials, induction therapies did not improve the complete resectability rate at the time of surgery despite downstaging a significant number of patients and improving overall survival.

Newer chemotherapeutic agents, proven effective in advanced lung cancer, can be administered more easily with greater patient tolerance. Current investigations are directed at employing these newer more tolerable drugs in combination with each other and with radiotherapy. A variety of induction treatments are currently being investigated including newer drug combinations with or without radiotherapy and shorter induction treatments utilizing accelerated hyperfractionation radiotherapy techniques. Because of the apparent advantage of induction therapy plus surgery in locally advanced (IIIa) disease, this treatment is now being assessed in earlier stage tumors. Other than T1No lung cancer, those patients clinically staged as T2No (stage Ib) or greater have less than a 50% 5-year survival following surgical. As with the more locally advanced stage IIIa tumors, the commonest sites of recurrence are distant. The theoretical advantages of induction therapy, compared to adjuvant treatment to control such distant micrometastatic sites, are obvious. These include: 1) Chemotherapy prior to surgery appears more tolerable for the patient than in an adjuvant setting, 2) the micrometastatic disease is treated earlier rather than later, 3) compared to adjuvant therapies, patients receiving induction therapies usually receive all the treatment planned, 4) patients following surgery have lower immunologic parameters which may adversely affect the ability of the chemotherapy given postoperatively to be as effective. For these reasons, with the more tolerable newer agents, induction

therapies prior to surgical resection for these earlier stage lung cancers are being investigated worldwide. Two recent North American and European trials have demonstrated that these approaches are feasible and the latter trial has suggested an advantage in survival forthe early stage patients receiving the combined modality therapy.

Because of the similar successes of chemoradiation (vs radiotherapy alone) as primary treatment for locally advanced disease, a North American Intergroup trial is now comparing a non-surgical treatment (chemoradiation alone) to induction chemoradiation plus surgery for patients with preoperatively identified stage IIIA (N2) disease, (utilizing cisplatin and etoposide) and many European groups are initiating similar studies.

QUESTIONS TO BE ANSWERED IN THE FUTURE

1.Which is the appropriate presurgical induction therapy-chemotherapy alone or combined with radiation? Only one trial has compared induction chemotherapy to induction chemoradiotherapy followed by surgery. This trial was reported in abstract form over 5 years ago-no paper has ever been published with the final results. In the fully reported phase II trials, median survival, 2 year survival and estimated 5 year survivals appear similar no matter the induction therapy.

2. Chemoradiotherapy or chemotherapy followed by chemoradiotherapy as induction? When chemoradiotherapy is used as primary treatment, in most series, induction chemotherapy followed by chemoradiotherapy has been employed. There is no firm evidence as yet to conclude whether simple concurrent chemoradiotherapy or induction chemotherapy followed by concurrent chemoradiotherapy is best when patients are ultimately treated by surgery. The former approach would certainly shorten the treatment time.

3. What is the role of surgery for post-induction persisting N2 disease? If patients are not down-staged following surgical resection in those patients who have persisting N2 disease at the time of surgery is disappointing (<10%). In some centers, persisting “bulky” N2 diesease following induction therapy negates a surgical treatment-these patients are treated with radiotherapy for primary control rather than surgery. This persisting N2 disease can be identified by repeat mediastinoscopy or perhaps by PET scanning, thus avoiding a major surgical incursion for little yield.

4. Following induction therapy and surgery, what is the role of adjuvant treatments? In most induction therapy trials, postoperative therapies have been added including additional chemoradiotherapy, additional chemotherapy or adjuvant radiotherapy. The role of these adjuvant therapies have never been assessed. In the few trials where adjuvant therapies were not mandated, the results appear comparable to those where adjuvant therapies were used.

5. What is the role for right pneumonectomy following induction therapies? Although never reported in detail, most reports suggest that patients undergoing right pneumonectomy following induction therapies have a higher morbidity including episodes of ARDS and bronchopleural fistula and thus a higher postoperative mortality rate. In most centers, right pneumonectomy is avoided wherever possible. When this resection is required, should surgery be avoided?

6. What is the role of induction therapies in stage IIIb disease? When clinically unsuspected T4 tumors are resected, postoperative adjuvant therapies have been standart treatment. Surgery as a treatment for clinically apparent T4 or N3 disease is very controversial. In most instances, clinically identifid stage IIIb disease is treated primarily with chemoradiotherapy. However, there have now been phase II trials investigating the role of chemoradiotherapy for this stage of disease. Few trials of induction chemotherapy have taken place since surgeons recognized that radiotherapy impoves local control-a significant problem in this more advanced stage III group. The exact role of surgery and the role of induction therapies in these more advanced T4 and/or N3 tumors has yet to be investigated in other than phase II trials or retrospective reports. Unfortunately, all of these induction trilas depend on clinical staging which is notoriously inaccurate, often overstaging T4 disease.

SUMMARY

In those locally advanced stage IIIa N2 tumors that can be completely excised, surgical treatment still appears to offer a good therapeutic option. Exciting new developments suggest that induction therapy (chemotherapy or chemoradiotherapy) may provide improved survival for these patients. In stage IIIa disease, this approach should be compared to chemoradiotherapy with and without surgery before an answer is reached as to what is the best treatment for this stage of lung cancer.