

NONSURGICAL ADJUNCTS TO THE TREATMENT OF ESOPHAGEAL CANCER

Introduction

- Incidence is rising, but still uncommon 1% of total cancer
- Mortality is high—13,000 deaths per year
 - Advanced stage of presentation
 - >60% thought ineligible for treatment with curative intent
- Advanced presentation
 - Largely asymptomatic until large enough to obstruct lumen
 - Even small submucosal tumors—LN metastasis in 40% of cases
 - Mucosa/submucosa drained by rich network of transmural lymphatics that quickly transport malignant cells to regional LN and beyond
 - Local infiltration of surrounding organs such as aorta, trachea, bronchus common due to lack of esophageal serosa and its location in tight mediastinal space
- Patients are malnourished, cachectic, and cannot swallow solid foods
- Needs for multimodality therapy
 - Surgery is best single modality therapy compared with radiation and chemo
 - Surgery alone with local and distant failure rate of 50% and 5 year survival < 25%
 - Underscores the need for multimodal therapy w/ chemoradiation to improve local and distant failure

Adjuvant radiotherapy

- Either preoperative (neoadjuvant) or post-operative (adjuvant)
- Pre-operative radiotherapy
 - Serves to eradicate viable cancer cells, ensuring that the cells are not widely disseminated with surgical disruption of blood vessels and tissue planes
 - Shrinks the size of tumor, enabling complete resection of malignancy
 - Not supported by literature for superior local control (some suggestion of improved local control in one trial, but not statistically significant), or prolonged pt survival
 - *6 prospective randomized trials comparing pre-op radiation to surgery*
 - *4/6 with no survival benefit; 1 had confounding variables because patients received chemo, 2nd have no rigorous statistical analysis of data*
 - *several non-randomized trials and metaanalysis of 1147 demonstrated no improved survival*
- Post-op radiation
 - Theoretically decreases post-op recurrence
 - Only two prospective randomized trials
 - No improvement in patient survival
 - One study suggested decrease in local failure rate for lymph node-negative disease but no benefit in patients with lymph node positive disease
 - Studies performed on patients with squamous cell cancer because deemed more sensitive to radiotherapy
 - Generally has a role in patients with positive surgical margins; combined with systemic chemotherapy

Definitive radiation

- Usually reserved only for patients who cannot tolerate chemotherapy because it has been proven in randomized trials to be inferior to chemoradiation
- Radiation alone: median survival 6-12 months, 5-year survival <10%, local failure rates 68-74% (primary reason for failure)

Definitive chemoradiation

- Cisplatin/5FU
- Superior to radiation alone in several randomized trials
- Local control rate and survival similar to surgery alone
- Local control rates between 40-75%, median survival between 9-24 months, and 5-year survival 18-40%
- many oncologists believe that surgery is unnecessary and chemoradiation is most important aspect of treatment
 - though direct comparisons to surgery have been attempted, both trials failed because of physicians' reluctance to accept non-surgical approach in patient who are operative candidates
 - there are reports of "salvage" esophagectomy — esophagectomy only with treatment failure. Surgery much more difficult and post-op morbidity high. No randomized trials
- Generally reserved for patients who are non-surgical candidates

Adjuvant chemotherapy

- Downstage tumor and eradicate micrometastasis in lymph node or systemic circulation
- Usually administered in combination therapies
- Multiple trials of pre-operative therapy have not lived up to promise
 - Generally failure of patients to respond to chemotherapy
 - 4/5 randomized trials comparing adjuvant post-operative chemo vs surgery alone showed no survival benefit
 - Kelson et al from Memorial in 1998 largest trial that enrolled 200 patients, both pre-operative and post-operative chemo cisplatin 5-FU → no survival benefit
 - potential controversy: UK trial of 802 patients of cisplatin 5FU/surgery with initial results showing improved median survival (17 vs. 13, p=0.003) and overall survival. May affect thinking once completed because chemotherapy generally better tolerated than chemoradiation
- Two findings
 - Pretreatment weight loss is a significant predictor of poor outcome
 - Complete and partial responders to chemotherapy survived longer than nonresponders
- Post-op chemotherapy
 - One trial Ando et al 1997 for SCC thoracic esophagus → no survival benefit
 - Difficult for patients to tolerate post-op chemo—too frail

Neoadjuvant chemoradiation

- Rationale for use is the failure of adjuvant radiation, adjuvant chemoradiation, or surgery alone to control the high rate of local and distant recurrences in pts w/ esophageal cancer
 - In combination, independent tumor activity of each therapy is optimized without summation of toxic effects
 - Synergistic effect of two modalities because chemotherapy acts as a radiosensitizer and vice versa
 - Continuous infusion cisplatin and protracted venous infusion 5-FU (commonly used for esophageal cancer) thought to act in this way
 - Chemoradiation more tolerable pre-operatively than post-operatively
 - Some evidence that pre-operative therapy permits higher resectability in subsequent surgery
 - Preliminary data suggests that neoadjuvant chemoradiation is first adjuvant approach for esophageal cancer that demonstrates improved survival over surgery alone, especially in subset of patients with complete response and no pathologic evidence of residual disease
- Single institution trials have suggested superior local control and survival
- Randomized trials are inconclusive
 - Differences in treatment regimens and patient selection—difficult to interpret outcome data
 - Difficult to perform randomized multicenter trials because of lack of consensus on treatment regimens
 - Comparison to surgery alone not possible
 - ? improved overall survival: 3 randomized trials
 - Walsh et al 1996 Irish trial
 - 3-year survival 32 vs. 6 %, median survival 16 vs. 11 months
 - criticized for low survival in surgical arm possibly due to inaccurate pre-op staging, high surgical mortality 9%
 - Urba et al 201 Michigan showed survival improvement (30% vs 16%) which was not statistically significant, median survival same 17%; there was a significant reduction of local and regional recurrence
 - Bosset et al 1997
 - no overall survival benefit
 - improved cancer survival in the multimodality arm was offset by increased postoperative mortality. Postoperative deaths were pulmonary in nature and may be related to the radiation treatment. The radiation schedule (split course) is now known to be suboptimal for cancer treatment and the fractionation (large fractions) predisposes to postoperative ARDS.
 - improved disease-free survival
 - Complete responders have significantly improved survival compared to non-responders (CR rates average 25%)
 - Suggestion that partial response with tumor down staging also results in improved survival
 - Search for molecular markers that predict complete response pre-therapeutically

- Search for increasing potent regimens that may achieve higher pathologic response rates
 - Paclitaxel—potent radiosensitizer; leads to higher pathologic response rates
 - Intensification of radiotherapy with brachytherapy—leads to increased toxicity
 - Need to balance increased potency with increased acute toxicity

Conclusions

- Need multimodality therapy to prevent local and distant treatment failure
- Definitive chemoradiation for unresectable tumors. ? potential as definitive treatment
- Neoadjuvant chemoradiation for resectable tumors is future of esophageal cancer treatment

References

1. Koshy M et al. Multiple Management Modalities of Esophageal Cancer: Combined Modality Management Approaches. *Oncologist*, Jan 2004; 9(2): 147-159.
2. Feig et al. *The MD Anderson Surgical Oncology Handbook, 3rd Edition*. Lippincott Williams & Wilkins, 2003; Pages 145-157.
3. Cameron J. *Current Surgical Therapy*. Elsevier Mosby, 2004; Pages 55-57.

Ateet H. Shah, M.D.
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