Diagnostic Problems Following Preoperative Chemoradiation in the Upper GI Tract

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Bullet Points

• Patients with stage II, III, and IVa carcinomas of the esophagus or GE junction are candidates for preoperative chemoradiation. Preoperative therapy often downstages the tumor and increases the likelihood of a complete resection. Both disease-free survival and overall survival are improved with neoadjuvant therapy.

• Chemoradiation also affects nearby benign tissues and can result in: 1) epithelial atypia of gastric glands mimicking dysplasia or intramucosal carcinoma, 2) residual endocrine cells in micronests or single cells within the lamina propria and muscularis mucosae, sometimes mimicking carcinoma or autoimmune atrophic gastritis, and 3) giant multinucleated squamous cells resembling HSV infection.

• Extent of residual carcinoma, post-therapy pathologic stage (ypT), and number of involved lymph nodes are all independent predictors of overall survival.

• Neuroendocrine differentiation in tumor cells seems to impart resistance to preoperative chemoradiation. Neuroendocrine differentiation in residual carcinoma is an independent predictor of worse disease-free survival.

• After pre-operative chemoradiation, residual signet-ring cell or mucinous histology (particularly acellular mucin pools) is an independent predictor of better overall survival. In contrast, this histology imparts a worse overall survival in patients who receive surgery alone.

Preoperative Therapy – Rationale

Survival after esophagectomy for carcinoma of the distal esophagus or gastroesophageal junction is poor when surgical therapy is used in isolation. Many of these patients will develop either local recurrence or distant metastases. The use of radiation (or chemoradiation) alone is even less successful than surgery in achieving local control. Preoperative (neoadjuvant) chemoradiation followed by esophagectomy takes advantage of the radiosensitizing properties of chemotherapy and allows for a reduction in tumor size that makes subsequent complete resection of the tumor more likely. Exact protocols for preoperative chemoradiation vary among institutions, but a common protocol includes concomitant external beam radiation (for a total dose of 4500-5040 cGy in 25 or 28 fractions) and two cycles of chemotherapy using 5-FU and cisplatin (mitomycin, vinblastine, irinotecan, and paclitaxel have also been used).1-3 Induction chemotherapy is sometimes given prior to concurrent chemoradiation. Curative esophagectomy then takes place following restaging at 4 – 6 weeks after completion of chemoradiation.

In a recent meta-analysis of neoadjuvant therapy for esophageal carcinoma, Gebski et al. showed significant survival benefits for preoperative chemoradiation in both adenocarcinomas and squamous cell carcinomas, and for preoperative chemotherapy in adenocarcinomas.4 At 2 years, there was an actuarial survival benefit of 13% in patients treated with preoperative chemoradiation vs. surgery alone, meaning that preoperative treatment of 8 patients would be expected to save one extra life relative to surgery alone.4
Accurate staging of patients prior to therapy is essential, because patients with T1N0 disease do not need neoadjuvant chemoradiation, and patients with T4 or M1b disease do not benefit. Additionally, there is no support for postoperative chemoradiation.

The remaining discussion focuses on diagnostic problems that can arise when evaluating the resection specimen itself, and when evaluating biopsy specimens of the esophagus and stomach that may be taken during chemoradiation, during restaging, or during surveillance after surgery.

Effects of Chemoradiation on Non-Neoplastic Tissues

Endocrine Cell Pseudo-Hyperplasia Mimicking Residual Tumor or Autoimmune Gastritis

Endocrine cells are normally present in both the gastric cardia and fundus. Fundic mucosa contains a variety of endocrine cell types, but most represent enterochromaffin-like (ECL) cells that secrete histamine in response to gastrin. In biopsies from endoscopically normal cardia, Voutilainen et al. identified low- to moderate numbers of serotonin-positive endocrine cells in essentially all cases.5 Neuroendocrine cells are relatively resistant to the effects of chemoradiation and can remain behind when other benign glandular cells are destroyed.

In a recent study by Stewart and Hillery, endocrine cell nests and/or single endocrine cells were present in mucosa adjacent to tumor in 8/11 esophagectomy specimens after neoadjuvant therapy; in comparison, only 2/10 cases that did not receive neoadjuvant therapy had rare single endocrine cells and none had endocrine nests.6 These cells are found in the deep lamina propria and in muscularis mucosae, where they can cause confusion with residual carcinoma, particularly in biopsy specimens. The mucosa above the “pseudo-hyperplastic” endocrine cells typically contains a lymphoplasmacytic infiltrate and cardia-type glands +/- oxyntic glands, with therapy-induced cytologic atypia and mild, moderate, or severe atrophy. These changes are not present in mucosa distant from the treatment field.

Recognition of this phenomenon is needed to avoid overinterpretation as either residual tumor or autoimmune gastritis. In cases that are worrisome for carcinoma, chromogranin immunostaining may help to demonstrate the neuroendocrine nature of the cells, although endocrine cell nests are usually recognizable by H&E stain. The lack of cytologic atypia in the endocrine cells helps to distinguish them from residual tumor with neuroendocrine differentiation (a phenomenon discussed below). Finally, these benign endocrine cells are usually not found in association with intestinal metaplasia/Barrett mucosa as most adenocarcinomas are, but rather in association with cardia-type or cardio-oxyntic-type mucosa.

Glandular atrophy, lamina propria inflammation, and neuroendocrine hyperplasia in the deep lamina propria and muscularis mucosae also characterize autoimmune atrophic gastritis. There are two main features that distinguish treatment effect from autoimmune gastritis. Most importantly, these changes occur diffusely throughout the body and fundus in patients with autoimmune gastritis but are only present near the treatment field in patients with carcinoma. Second, patients with autoimmune gastritis usually have true, nodular endocrine cell hyperplasia whereas the endocrine cells in treated carcinoma patients are single or form “micronests.”
**Therapy Effect in Benign Glands**

Brien et al. described the histologic features of therapy-induced reactive epithelial atypia in gastric mucosa, a process they termed “gastric dysplasia-like epithelial atypia” because the changes are easily overinterpreted as dysplasia or even intramucosal adenocarcinoma. Both gastric glands and foveolar cells (or occasionally only the glands) show nuclear pseudostratification, enlargement, and hyperchromatism; and there may be clumping of chromatin, prominent nucleoli, and even increased N:C ratios. Frequent mitoses are common but it is unusual to see atypical mitotic figures. The gastric glands are often atrophic and form irregular “microcysts” lined by flattened glandular cells. Some features that can help to distinguish therapy-induced reactive atypia from true gastric dysplasia include lack of intestinal metaplasia; microcystic change; lack of mitoses at the surface epithelium; retention of nuclear polarity; cytoplasmic hypereosinophilia; and vacuolization of the glands. Another important feature is the location of the atypia – in true gastric dysplasia the atypia is limited to the foveolar cells whereas both gastric glands and foveolar cells are affected in patients who have received chemoradiation. Immunohistochemically, reactive mucosa lacks over-expression of p53 and shows normal containment of MIB-1 staining to the deep foveolar neck cells. In Brien et al.’s study, dysplasia-like changes were seen in the gastric mucosa in 7.5% of patients who had received neoadjuvant therapy for esophageal carcinoma, and is not present in untreated cases.

**Giant, Multinucleated Squamous Cells Mimicking Viral Infection**

Patients receiving neoadjuvant therapy are, obviously, immunosuppressed and can suffer from odynophagia and esophagitis that lead to upper endoscopy and biopsy. Occasionally, biopsies from the squamous esophagus contain a few or many multinucleated giant cells that superficially resemble HSV-infected cells. These cells are not specific to radiation alone, and can be seen in varying types of esophagitis. In a study of 14 esophageal biopsies with multinucleated giant cells by Singh and Odze, etiologies included reflux esophagitis (10 patients), Candida esophagitis (1 patient), alendronate (1 patient), and radiation (1 patient). In another study of alendronate-induced esophagitis, multinucleated giant cells were seen in 3 of 10 cases. These giant cells have perinuclear halos and eosinophilic nucleoli but no true nuclear inclusions, and are negative for HSV-1, HSV-2, CMV, and HPV by immunostaining. Unlike HSV infections, the giant cells are not restricted to the periphery of vesicles or ulcers but can be found throughout the epithelium; in fact, many cases do not have any erosion or ulceration and instead have multinucleated giant cells in mucosa that is just erythematous.

**Effects of Chemoradiation on Carcinomas**

**Staging of Residual Carcinoma**

The aim of neoadjuvant therapy is to downstage or even eliminate viable tumor cells prior to surgery. In two large studies of 108 and 239 patients who received preoperative chemoradiation, there were complete response rates (no residual tumor) of 22% and 29%, respectively. There have been several schemes developed to semi-quantitate the amount of residual carcinoma and therefore assess the effect of preoperative chemoradiation. These systems generally compare the area of viable carcinoma cells or glands to the area of mural fibrosis, with the assumption that mural fibrosis is a marker for prior tumor. One recent system for grading chemotherapy effect was developed by Chirieac et al. at M. D. Anderson Cancer Center and
consists of 3 categories: 1) No residual carcinoma, 2) 1%-50% residual carcinoma (individual viable tumor cells or microscopic foci of tumor at the primary site), and 3) >50% residual carcinoma (substantial amounts of residual carcinoma, often grossly visible). With multivariate analysis the authors showed that there were 2 independent predictors of outcome: Extent of residual carcinoma predicted overall survival, and post-therapy pathologic stage predicted both disease-free survival and overall survival. Further, grading of the extent of residual carcinoma and post-therapy pathologic staging (ypT) are both highly reproducible among pathologists. Wu et al. showed that there is excellent interobserver agreement in grading extent of residual carcinoma (kappa = 0.84) and good interobserver agreement in assigning the ypT stage (kappa = 0.71).

Unless there is grossly visible residual tumor, accurate measurements of residual carcinoma extent and ypT stage are dependent upon submission of the entire tumor bed/ulcer site for pathologic evaluation.

The number of regional lymph node metastases is also an independent predictor of survival after chemoradiation. Five-year overall survival rates for patients with one positive lymph node are similar to patients without lymph node metastases regardless of their post-therapy pathologic tumor status (34% survival vs. 38% survival, p = 0.84), but significantly higher than the 5-year overall survival in patients with >2 involved lymph nodes (34% vs. 6%, p = 0.02).

**Morphologic Features After Chemoradiation**

Dunne et al. detailed the morphologic changes in both adenocarcinomas and normal tissues following chemoradiation. When there is chemoradiation response with little remaining tumor, the tumor cells are often present as single cells in a densely fibrotic stroma, or as small tubules and lines of cells. Cytologically, the cytoplasm can be vacuolated or densely eosinophilic, and adjacent tumor cells can show merging of their cytoplasm. Nuclei are described as “popcorn-like” – multilobated with bizarre shapes.

The surface mucosa is usually ulcerated with a prominent lymphoplasmacytic infiltrate in the submucosa. One potential mimic of residual tumor is chemoradiation-induced cytologic atypia of the esophageal submucosal glands, which can also show squamous metaplasia. Their lobulated architecture and location in the submucosa should help to distinguish esophageal glands from carcinoma.

**Neuroendocrine Differentiation After Chemoradiation**

Neuroendocrine cells (identified by positivity for chromogranin immunostaining) have been reported in 61.8% - 68% of Barrett mucosa regardless of the presence or absence of dysplasia. In the latter study, encompassing resection specimens from a patient population that was mainly treated by surgery without neoadjuvant chemoradiation, neuroendocrine cells were also detected in 49% of GE junction adenocarcinomas – mostly as scattered cells or in small nests, with only ~ 4% of tumors having >20% positivity. In the former study, where somewhat more than half of the patients received neoadjuvant therapy, 20.7% of esophageal adenocarcinomas contained neuroendocrine cells. Neither study showed a discernable effect on survival from the presence or absence of neuroendocrine cells.

In a recent study comprised completely of patients who had received preoperative chemoradiation for adenocarcinomas of the esophagus and GE junction, neuroendocrine differentiation was seen in 52% of resection specimens containing residual tumor.
patients with paired pretreatment biopsies and post-treatment esophagectomies, the proportion of tumor cells with neuroendocrine differentiation had increased from a mean of 6% to a mean of 47%, suggesting that tumor cells with neuroendocrine differentiation are more resistant to chemoradiation. In fact, ~20% of residual carcinomas had widespread neuroendocrine differentiation, with >50% of tumor cells labeling for chromogranin and/or synaptophysin. Unlike the two studies discussed above, tumors with neuroendocrine differentiation after chemoradiation had significantly worse disease-free survival in multivariate analysis, independent of post-therapy staging and extent of residual tumor.

Mucinous or Signet-Ring Cell Changes After Chemoradiation

The prevalence of signet-ring cell or mucinous histology is nearly identical in treated or untreated esophageal/EG junction adenocarcinomas. However, the significance of histology depends on whether the patient has received preoperative chemoradiation or surgery alone. In esophagectomies without preoperative chemoradiation, the presence of mucinous or signet ring morphology is a significant, independent adverse predictor of overall survival. For example, in patients with negative specimen margins, median survival was 39.6 months for adenocarcinomas of the usual type but only 16.2 months for mucinous/signet ring histology.

In contrast, when there has been preoperative chemoradiation and the esophagectomy specimen contains only acellular mucin pools, overall survival is significantly better than when there is a complete response but no acellular mucin pools. In the study by Chirieac et al., 13 patients with acellular mucin pools were all alive after a median follow-up of 36 months. However, the presence of mucinous or signet ring morphology in patients with residual tumor after chemoradiation had no effect on survival.

REFERENCES


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USCAP 2008

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Trends in Esophageal/GE Junction and Non-Cardia Gastric Carcinoma

Reproduced from Lau et al. *Am J Gastroenterol.* 2006;101:2485-92
Neoadjuvant Chemoradiation: Rationale

• Surgical therapy alone associated with poor survival, risk of locoregional recurrence, and metastatic disease

Example of mortality rates for gastric CA – little change over 20 yrs

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Neoadjuvant Chemoradiation: Rationale

- Preoperative chemoradiation may:
  - provide early therapy for undetected distant metastases
  - shrink tumor size and depth of invasion (increasing chance of complete resection with negative margins)
  - downstage disease (even eliminating regional lymph node metastases)
Survival Benefit From Neoadjuvant Chemoradiation in a Meta-Analysis

Figure 4. Mortality estimates for neoadjuvant chemoradiotherapy compared with surgery alone, by tumour type and by sequence of treatment regimen
CRX=chemoradiotherapy. *Although CI is close to 1·0, p=0·04 due to rounding up. †Only studies published in peer-reviewed journals. ‡Published and unpublished studies. Figure excludes patients with unavailable histology.

Treated Esophageal Adenocarcinoma with Ulceration (photo courtesy of Tsung-Teh Wu, M.D., Ph.D.)
Effects of Chemoradiation

• On benign tissues:
  – Esophageal ulceration
  – Reactive atypia incl. giant multinucleated squamous cells
  – Gastric glandular atypia (can resemble dysplasia)
  – Gastric endocrine pseudohyperplasia (can resemble Type A gastritis)
Treated Esophageal Adenocarcinoma with Ulcer Site
Dense Plasmacytic Inflammation Following Chemoradiation
Giant Multinucleated Squamous Cells Following Chemoradiation (HSV negative)
Chemoradiation-Induced Squamous Metaplasia and Reactive Atypia in Submucosal Glands
Effects of Chemoradiation

- On tumor:
  - Dense fibrosis +/- residual tumor cells
  - Morphologic alterations of tumor cells
    - Single cells
    - Small tumor nests or microglands
    - Bizarre nuclei
    - Neuroendocrine differentiation
    - Mucinous or signet ring histology
Tumor Bed – Dense Submucosal Fibrosis
Adenocarcinoma After Chemoradiation – Single Signet Ring Cells
Adenocarcinoma After Chemoradiation – Microglands with Densely Eosinophilic Cytoplasm
Adenocarcinoma After Chemoradiation – Bizarre, Multilobated Nuclei
Measuring the Impact of Preoperative Therapy

- Extent (%) of residual tumor
- Post-therapy pathologic staging
Grading Extent of Residual Carcinoma after Chemoradiation

Fig. 4. Probability of disease-free survival (death from any cause) in 24 patients with CR as compared to 84 patients with RT following neoadjuvant therapy and esophagectomy. Zero time on the abscissa represents the date of esophagectomy. CR, complete pathologic response; RT, residual tumor.

Extent of Residual Carcinoma Significantly Impacts Survival

FIGURE 1. Overall survival of resected esophageal cancer patients treated with preoperative chemoradiation and surgery according to pathologic response at primary tumor (pP) (3 years: P0 = 0% residual = 74%; P1 = 1%–50% residual = 54%; P2 = >50% residual = 24%, P < 0.001).

Post-therapy Staging (ypT) for Esophageal and GEJ Carcinomas

- Similar to the “usual” staging system
  - T0 (complete response)
  - T1 (mucosal or submucosal invasion)
  - T2 (muscularis propria)
  - T3 (adventitia)
  - T4 (adjacent structures)
  - N1 (1+ regional LN)
  - M1a (celiac LN)
  - M1b (distant metastases)

AJCC 6th ed.
Extent of Residual Carcinoma and ypT Stage after Chemoradiation: Significant Impacts on Survival

Reproduced from Chirieac LR et al. Cancer 2005
No or 1 Positive Lymph Node After Chemoradiation: Significantly Better Survival Than 2 or More LN+

Reproduced from Gu Y et al. Cancer 2006
Regression of Lymph Node Metastasis with Chemoradiation (fibrosis and acellular mucin pools)
Neuroendocrine Differentiation in Residual Tumor: Negative Impact on Survival

Reproduced from Wang KL et al. *Cancer* 2006
Neuroendocrine Differentiation in Treated Tumor (photo courtesy of Tsung-Teh Wu, M.D., Ph.D.)
Acellular Mucin Pools After Chemoradiation: Positive Impact on Survival

Reproduced from Chirieac LR et al. Clin Cancer Res 2005
Mucinous or Signet-Ring Cell Histology with Surgery Alone: Adverse Impact on Survival

Reproduced from Chirieac LR et al. Clin Cancer Res 2005
Mucinous or Signet-Ring Cell Histology with Residual Carcinoma: No Impact on Survival

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  • Gastric glandular atypia
    (can resemble dysplasia)
  • Gastric endocrine pseudohyperplasia
    (can resemble Type A gastritis)
Treated esophageal CA with ulcer site
Dense plasmacytic inflammation
“Bizarre stromal cells”: upper eso ulcer + stricture in 50 y/o M
“Bizarre stromal cells” mimicking viral effect
“Bizarre stromal cells” mimicking carcinoma
Immunostaining: vimentin+, keratin-, etc.
Multinucleated squamous cells: UGI bleeding in 69 y/o M
Multinucleated Epithelial Giant Cells

Multinucleated Epithelial Giant Cell Changes in Esophagitis: A Clinicopathologic Study of 14 Cases

Author(s): Singh, Surendra P. M.D.; Odze, Robert D. M.D., F.R.C.P.C.

# Multinucleated Epithelial Giant Cells

<table>
<thead>
<tr>
<th>Age (yr)/sex</th>
<th>Symptoms</th>
<th>Clinical diagnosis</th>
<th>Endoscopic findings</th>
<th>Treatment</th>
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<td>1</td>
<td>57/M Abdominal pain</td>
<td>GERD</td>
<td>Erythema</td>
<td>Antibiotics</td>
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<td>2</td>
<td>65/F UGIB</td>
<td>GERD, HSV?</td>
<td>Ulcer</td>
<td>Acyclovir, omeprazole</td>
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<td>60/F Heartburn</td>
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<td>76/M UGIB</td>
<td>GERD</td>
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<td>5</td>
<td>53/M UGIB</td>
<td>GERD</td>
<td>Ulcer</td>
<td>Omeprazole, H2 blocker</td>
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<td>61/M Dysphagia, odynophagia</td>
<td>Candida esophagitis</td>
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<td>Radiation esophagitis</td>
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<td>Omeprazole</td>
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<td>Ulcer</td>
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<td>GERD</td>
<td>Stricture</td>
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<td>12</td>
<td>83/F Abdominal pain, heartburn</td>
<td>GERD</td>
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<td>13</td>
<td>74/F Dysphagia</td>
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<td>14</td>
<td>47/F UGIB</td>
<td>GERD</td>
<td>Ulcer</td>
<td>Omeprazole, acyclovir</td>
</tr>
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UGIB, upper gastrointestinal bleeding; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus infection.
Cardia bx during restaging: 60 y/o F
Glandular atypia
Gastric Dysplasia-Like Epithelial Atypia Associated with Chemoradiotherapy for Esophageal Cancer: A Clinicopathologic and Immunohistochemical Study of 15 Cases

Thomas P. Brten, M.D., Francis A. Farraye, M.D., Robert D. Odze, M.D., F.R.C.P.(c)

Departments of Pathology (TPB, RDO) and Gastroenterology (FAF), Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Preoperative chemotherapy combined with radiotherapy (chemrad) is a common type of neoadjuvant treatment for esophageal adenocarcinoma or squamous cell carcinoma. The purpose of this study was to describe the clinical, histologic, proliferative (MIB-1), and oncogenetic (p53) features of 15 patients with gastric dysplasia-like epithelial atypical changes associated with preoperative chemrad for esophageal cancer. Two of these cases were initially diagnosed as well-differentiated squamous cell carcinoma. Pathologists should be aware of this entity and its histologic and immunohistochemical features to avoid misinterpretation and prevent unnecessary treatment.

KEY WORDS: Atypia, Chemotherapy, Dysplasia, Esophageal cancer.

Cited: Mod Pathol 2001;14(5):389–396
# Epithelial Atypia After Chemoradiation

## TABLE 1. Summary of the Pathologic Features of the Study Cases and Controls

<table>
<thead>
<tr>
<th>Features</th>
<th>Study Cases, $n = 15$ (%)</th>
<th>Dysplasia Controls, $n = 12$ (%)</th>
<th>$P$ Value</th>
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<tbody>
<tr>
<td><strong>Anatomic distribution</strong></td>
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<td></td>
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<tr>
<td>Flat appearance</td>
<td>15 (100)</td>
<td>8 (67)</td>
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<td>Foveolar and glandular atypia</td>
<td>14 (93)</td>
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<td>&lt; .001</td>
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<tr>
<td>Glandular atypia only</td>
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<tr>
<td>Foveolar atypia only</td>
<td>0 (0)</td>
<td>12 (100)</td>
<td>&lt; .001</td>
</tr>
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<td>Patchy distribution</td>
<td>14 (93)</td>
<td>1 (8)</td>
<td>&lt; .001</td>
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<td>Surface maturation</td>
<td>7 (50)</td>
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<tr>
<td>Nuclear pseudostratification</td>
<td>12 (80)</td>
<td>12 (100)</td>
<td>NS</td>
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<tr>
<td>Hyperchromasia</td>
<td>14 (93)</td>
<td>12 (100)</td>
<td>NS</td>
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<tr>
<td>Enlarged nuclei</td>
<td>14 (93)</td>
<td>12 (100)</td>
<td>NS</td>
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<tr>
<td>Pleomorphic nuclei</td>
<td>7 (47)</td>
<td>8 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>Clumped chromatin</td>
<td>3 (21)</td>
<td>11 (92)</td>
<td>&lt; .001</td>
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<tr>
<td>Prominent nucleoli</td>
<td>6 (43)</td>
<td>2 (17)</td>
<td>&lt; .05</td>
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<td>Increased nuclear/cytoplasmic ratio</td>
<td>4 (27)</td>
<td>8 (67)</td>
<td>NS</td>
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<tr>
<td>Loss of polarity</td>
<td>0 (0)</td>
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<tr>
<td>Multinucleation</td>
<td>0 (0)</td>
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<td><strong>Mitoses</strong></td>
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<tr>
<td>Frequent mitosesa</td>
<td>9 (60)</td>
<td>11 (92)</td>
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<td>Mitoses in upper foveolae or surface epithelium</td>
<td>0 (0)</td>
<td>8 (67)</td>
<td>&lt; .001</td>
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<td>Atypical mitoses</td>
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<td>5 (42)</td>
<td>= .04</td>
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<td><strong>Cytoplasmic features</strong></td>
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<td>Mucin depletion</td>
<td>14 (93)</td>
<td>12 (100)</td>
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<tr>
<td>Hypereosinophilia</td>
<td>13 (87)</td>
<td>0 (0)</td>
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<td>Vacuolization (glands only)</td>
<td>7 (47)</td>
<td>0 (0)</td>
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<td><strong>Glandular features</strong></td>
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<tr>
<td>Atrophy</td>
<td>7 (47)</td>
<td>8 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>Irregular microcystic change</td>
<td>11 (73)</td>
<td>0 (0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Adjacent gastric mucosa features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>2 (13)</td>
<td>12 (100)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Increased mononuclear inflammation only</td>
<td>6 (40)</td>
<td>4 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Increased mononuclear and neutrophilic inflammation</td>
<td>3 (20)</td>
<td>1 (8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Reproduced from Brien TP et al. *Mod Pathol* 2001;14:389-96
Vacuolization, hypereosinophilic cytoplasm, normal foveolar epithelium
Resection post-chemoXRT: EGJ CA
Glandular atrophy and nests in deep lamina propria
Synaptophysin immunostain
Endocrine Cell Pseudohyperplasia

ORIGINAL ARTICLE

Mucosal endocrine cell micronests and single endocrine cells following neo-adjuvant therapy for adenocarcinoma of the distal oesophagus and oesophagogastric junction

Colin J R Stewart, Simon Hillery

Endocrine Cell Pseudohyperplasia

- Endocrine nests +/- single cells in 8/11 resections post-chemoXRT
- Only 2/10 controls (single endocrine cells)

Table 2: Summary of pathology finding in resection specimens following neo-adjuvant therapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Resection specimen findings</th>
<th>LN positive/total examined</th>
<th>Tumour regression grade</th>
<th>Mucosal endocrine cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No residual mural tumour; mucin pools</td>
<td>1/7</td>
<td>Complete (grade 1)</td>
<td>SEC</td>
</tr>
<tr>
<td>2</td>
<td>No residual mural tumour; focal high-grade dysplasia; mucin pools</td>
<td>0/7</td>
<td>Complete (grade 1)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>PD adenocarcinoma extending to CRM</td>
<td>1/8</td>
<td>Partial &lt;50% (grade 4)</td>
<td>ECM</td>
</tr>
<tr>
<td>4</td>
<td>MD adenocarcinoma extending to CRM</td>
<td>-</td>
<td>Partial &gt;50% (grade 3)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>No residual mural tumour</td>
<td>1/8</td>
<td>Complete (grade 1)</td>
<td>ECM and SEC</td>
</tr>
<tr>
<td>6</td>
<td>Focal tumour in muscularis propria; CMV noted</td>
<td>2/15</td>
<td>Partial &gt;50% (grade 2)</td>
<td>SEC</td>
</tr>
<tr>
<td>7</td>
<td>No residual mural tumour</td>
<td>3/3</td>
<td>Complete (grade 1)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>No residual mural tumour; mucin pools</td>
<td>0/4</td>
<td>Complete (grade 1)</td>
<td>ECM</td>
</tr>
<tr>
<td>9</td>
<td>PD adenocarcinoma extending to CRM</td>
<td>0/8</td>
<td>Partial &lt;50% (grade 4)</td>
<td>ECM</td>
</tr>
<tr>
<td>10</td>
<td>PD adenocarcinoma extending to CRM</td>
<td>4/14</td>
<td>Partial &lt;50% (grade 4)</td>
<td>ECM and SEC</td>
</tr>
<tr>
<td>11</td>
<td>PD adenocarcinoma extending to CRM</td>
<td>1/12</td>
<td>Partial &gt;50% (grade 3)</td>
<td>ECM and SEC</td>
</tr>
</tbody>
</table>

LN, lymph nodes; MD, moderately differentiated; PD, poorly differentiated; CRM, circumferential (radial) resection margin; CMV, cytomegalovirus; SEC, single endocrine cells; ECM, endocrine cell micronests.

Reproduced from Stewart CJ and Hillery S. J Clin Pathol 2007;60:1284-9
• Nests = residual endocrine cells post-therapy induced glandular atrophy
• Can be mistaken for:
  • Residual adenocarcinoma
  • Type A (autoimmune) gastritis
Effects of Chemoradiation

• **On tumor:**
  • Dense fibrosis +/- residual tumor cells
  • Morphologic alterations of tumor cells
    • Single cells
    • Small tumor nests or microglands
    • Bizarre nuclei
    • Neuroendocrine differentiation
    • Mucinous or signet ring histology
Dense fibrosis with single residual tumor cells
A pathological study of tumour regression in oesophageal adenocarcinoma treated with preoperative chemoradiotherapy

B Dunne, J V Reynolds, E Mulligan, A Kelly, M Griffin

Abstract

Aims—To measure residual tumour in oesophageal adenocarcinoma treated with preoperative chemoradiotherapy, to correlate specific pathological variables with survival, and to describe morphological changes in tumour and non-neoplastic tissue resulting from preoperative treatment.

Methods—Resection specimens from 47 cases of oesophageal adenocarcinoma treated with preoperative 5-fluorouracil/cisplatin and radiotherapy were reviewed. The 5-year survival of approximately 20% after curative resection. Neoadjuvant chemoradiotherapy in addition to surgery for oesophageal carcinoma was shown to prolong survival in a prospective randomised trial from our unit and in some non-randomised trials. However, there remains considerable debate in the literature, and further randomised trials are needed before multimodal treatment can be established as the definitive approach. There is at present no accurate way of predicting which patients will benefit from this treatment approach and which will undergo potentially
Tumor cells after chemoradiation
Tumor cells after chemoradiation
Tumor cells after chemoradiation - single signet ring-like cells
Bizarre multilobated nuclei and merging of cytoplasm
Regression of Lymph Node Metastasis (fibrosis and acellular mucin pools)
Rare residual tumor cells in lymph node after chemoradiation
Squamous metaplasia and atypia in esophageal submucosal glands
Squamous metaplasia and atypia in esophageal submucosal glands
Chemoradiation-Induced Metaplasia

- Neuroendocrine differentiation (-impact)
- Mucinous/signet ring histology (+impact)
Neuroendocrine Differentiation

- Barrett’s esophagus (BE)

- Untreated esophageal CA

- No survival difference
Neuroendocrine Differentiation

• Neuroendocrine cells increase after treatment:
  • 6% cells vs 47% cells
    (paired pre-treatment bxs and post-treatment resections)

• Negative impact:
  • Disease-free survival
  • Overall survival

Wang KL et al. *Cancer* 2006
Neuroendocrine Differentiation in Residual Tumor: Negative Impact on Survival

* Multivariate analysis p = 0.02

Reproduced from Wang KL et al. Cancer 2006
Neuroendocrine Differentiation in Treated Tumor (photo courtesy of Tsung-Teh Wu, M.D., Ph.D.)
Mucinous/Signet Ring Cell Differentiation

- No difference in treated and untreated cases (17% vs 18%)
- High concordance (91%) between pre-treatment bx and post-treatment resection
  - 5% “usual” adenoCA in bx → mucinous in resection
  - 4% mucinous/signet ring cells in bx → “usual” adenoCA in resection
- Worse overall survival if esophagectomy alone

Fig. 2 Kaplan-Meier curves of overall survival among patients with carcinoma of the esophagus and EGJ treated with surgery alone and patients treated with preoperative neoadjuvant chemoradiation followed by esophagectomy.
Mucinous/Signet Ring Cell Differentiation

• Signet ring cell or mucinous histology in residual CA post-neoadjuvant therapy:
  • No difference in survival

Mucinous/Signet Ring Cell Differentiation

- Acellular mucin pools in patients with CR
  - Better overall survival

Acellular Mucin Pools After Chemoradiation: Positive Impact on Survival

Measuring the Impact of Preoperative Therapy

- Extent (%) of residual tumor
- Post-therapy pathologic staging
Fig. 4. Probability of disease-free survival (death from any cause) in 24 patients with CR as compared to 84 patients with RT following neoadjuvant therapy and esophagectomy. Zero time on the abscissa represents the date of esophagectomy. CR, complete pathologic response; RT, residual tumor.

* CR = 22%

Grading Extent of Residual Carcinoma after Chemoradiation

Grading Extent of Residual Carcinoma after Chemoradiation

Excellent Interobserver Agreement on Grading the Extent of Residual Carcinoma After Preoperative Chemoradiation in Esophageal and Esophagogastric Junction Carcinoma: A Reliable Predictor for Patient Outcome

Tsung-Teh Wu, MD, PhD,* Lucian R. Chiriac, MD,† Susan C. Abraham, MD, † Alyssa M. Krasinskas, MD,§ Huamin Wang, MD, PhD,* Asif Rashid, MD, PhD,* Arlene M. Correa, PhD,∥ Wayne L. Hofstetter, MD,∥ Jaffer A. Ajani, MD,∥ and Stephen G. Swisher, MD∥

Abstract: The extent of residual carcinoma in resected esophageal cancer specimens after preoperative chemoradiation is a predictor of survival according to 3 groups: P0 (0% residual carcinoma), P1 (1% to 50% residual carcinoma), and P2 (>50% residual carcinoma). However, the interobserver variation and reliability of this classification has not been evaluated among different pathologists. Histologic hematoxylin and eosin-stained slides from 60 resected cases of esophageal adenocarcinoma allow a novel and early means of comparing outcomes after different neoadjuvant treatment regimens.

Key Words: esophagus, residual carcinoma, chemoradiation, interobserver agreement, prognosis predictor

(Am J Surg Pathol 2007;31:58-64)

* kappa = 0.84 (excellent interobserver agreement among 6 pathologists)
FIGURE 1. Overall survival of resected esophageal cancer patients treated with preoperative chemoradiation and surgery according to pathologic response at primary tumor (pP) (3 years: P0 = 0% residual = 74%; P1 = 1%–50% residual = 54%; P2 = >50% residual = 24%; \( P < 0.001 \)).

Extent of Residual Carcinoma Significantly Impacts Survival

Reproduced from Swisher SG et al. *Ann Surg* 2005
Post-therapy Staging (ypT)

- Similar to the “usual” staging system
  - T0 (complete response)
  - T1 (mucosal or submucosal invasion)
  - T2 (muscularis propria)
  - T3 (adventitia)
  - T4 (adjacent structures)
  - N1 (1+ regional LN)
  - M1a (celiac LN)
  - M1b (distant metastases)

AJCC 6th ed.
ypT Stage: Significant Predictor of Survival

- ypT stage has predictive value independent of % residual tumor

Reproduced from Chirieac LR et al. Cancer 2005
Conclusions

• Neoadjuvant therapy increasingly used for upper GI CA
• Need to:
  • Keep in mind effects of therapy on benign tissues
  • Staging of residual CA in resection specimens is paramount
    • Accurate evaluation requires total embedding of tumor bed (if no gross residual CA)
    • Even rare tumor cells have adverse prognostic implications
  • Histology of residual CA may not correspond to pre-treatment histology
  • Two types of “metaplasia” may have prognostic significance:
    • Neuroendocrine (adverse impact)
    • Acellular mucin pools (positive impact)
Thank you