Relationship between HER-2 overexpression and brain metastasis in esophageal cancer patients

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Abstract

AIM: To study if HER-2 overexpression by locally advanced esophageal cancers increase the chance of brain metastasis following esophagectomy.

METHODS: We retrospectively reviewed the medical records of esophageal cancer patients who underwent esophagectomy at University of Iowa Hospitals and Clinics between 2000 and 2010. Data analyzed consisted of demographic and clinical variables. The brain metastasis tissue was assayed for HER-2 overexpression utilizing the FDA approved Dako Hercept Test®.

RESULTS: One hundred and forty two patients were reviewed. Median age was 64 years (36-86 years). Eighty eight patients (62%) received neoadjuvant chemoradiotherapy. Pathological complete and partial responses were achieved in 17 (19%) and 71 (81%) patients. Cancer relapsed in 43/142 (30%) patients. The brain was the first site of relapse in 9/43 patients (21%, 95% CI: 10%-36%). HER-2 immunohistochemistry testing of the brain metastasis tissue showed that 5/9 (56%) cases overexpressed HER-2 (3+ staining).

CONCLUSION: HER-2 overexpression might be associated with increased risk of brain metastasis in esophageal cancer patients following esophagectomy. Further studies will be required to validate this observation.

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Brain metastasis from locally advanced esophageal cancer as the first site of disease relapse following multimodality treatment that includes chemotherapy, radiation therapy and esophagectomy is rare\(^\text{[3,4]}\). The incidence rate of brain metastasis, thought to be around 1%-5%, is derived from case series and autopsy reports\(^\text{[6,7]}\). Although the treatment goal of locally advanced esophageal cancer is to cure the disease, there is a high rate of disease relapse, whether locally or as distant metastasis, with the majority of relapses occurring in the liver, abdomen, lungs and bone\(^\text{[8,9]}\). Urbà et al\(^\text{[9]}\), showed that 65% of patients treated with concurrent chemotherapy and radiation therapy then esophagectomy had distant metastases rather than local recurrence upon relapse.

Multiple clinical and pathological features have been identified as prognostic factors in patients who receive concurrent chemoradiotherapy and esophagectomy. Factors including pathological complete response (pCR) to neoadjuvant treatment\(^\text{[10,11]}\), lower tumor grade and stage\(^\text{[8,9]}\), and smaller tumor length\(^\text{[9]}\), are associated with favorable outcomes. Other trials showed that larger tumors and perioperative chemotherapy or radiation therapy might be associated with a higher risk of subsequent brain metastases\(^\text{[11,12]}\). In breast cancer, other risk factors such as over expression of HER-2, a membrane bound tyrosine kinase, were shown to predispose to brain metastasis (hazard ratio: 4.23, \(P = 0.0007\))\(^\text{[13,14]}\).

HER-2 is over expressed in approximately 25% of esophageal cancers\(^\text{[15,16]}\) and is associated with a worse prognosis\(^\text{[17,18]}\). HER-2 receptor status became more clinically relevant after the ToGA trial showed that targeting HER-2 positive gastric and gastroesophageal junction tumors with Trastuzumab (Herceptin), a recombinant humanized monoclonal antibody that inhibits HER-2 receptor, combined with chemotherapy improved survival in patients with metastatic disease\(^\text{[19]}\). To our knowledge, there has been no correlation identified between esophageal cancer HER-2 receptor positivity and risk of brain metastasis.
reached). Median survival for the pPR patients was 28.8 mo (95% CI: 18.7-36.0). Although Figure 2 shows a survival difference for the patients who had pCR and pPR, this was not statistically significant ($P = 0.207$).

The total number of identified relapses was 43/142 (30.3%). Median follow up time was 11.8 mo (< 1-110 mo). Initial relapses occurred in the residual esophagus, paraesophageal lymph nodes, mediastinum, liver, peritoneum, lungs, bone or brain. Frequencies of relapses at various sites are summarized in Table 2. There were 9/43 (21%) relapses in the brain (95% CI: 10%-36%) with the following characteristics: cancer stage T3N1M0 (7/9), neoadjuvant chemotherapy and radiation therapy (7/9), pCR (1/9), adenocarcinoma (7/9), squamous cell carcinoma (2/9).

HER-2 immunohistochemistry staining of the brain metastasis specimens showed that 5/9 specimens (56%) overexpressed HER-2 (3+ staining). The rest of the specimens (4/9) did not stain for HER-2 (0 staining). Figure 3 shows brain metastasis specimens with 3+ and 0 staining.

Treatment of brain relapses included surgical resection (2 patients), stereotactic radiosurgery (SRS) (1 patient), surgical resection followed by SRS to the tumor bed (3 patients), and whole brain radiation (3 patients). Survival following diagnosis of brain relapse ranged from < 1-22 mo. Two patients who had brain surgery and SRS lived longer than others (18 and 22 mo).

Table 1 Characteristics of esophageal cancer patients who underwent esophagectomy

| Characteristics | $n$ (%) |
|-----------------|---------|
| Age on diagnosis of esophageal cancer (yr) | |
| Median | 64 |
| Range | 36-86 |
| Sex | |
| Male | 124 (87.3) |
| Female | 18 (12.7) |
| Smoking | |
| $< 100$ cigs/life | 33 (23.2) |
| $< 10$ pack-year | 9 (6.3) |
| $> 10$ pack-year | 87 (61.3) |
| Unknown | 13 (9.2) |
| Esophageal cancer type (path report) | |
| Adenocarcinoma | 118 (83.1) |
| Squamous cell carcinoma | 22 (15.5) |
| Small cell carcinoma | 1 (0.7) |
| GIST | 1 (0.7) |
| T classification | |
| T1 | 18 (12.7) |
| T2 | 19 (13.4) |
| T3 | 76 (53.5) |
| T4 | 2 (1.4) |
| Unknown | 27 (19) |
| N classification | |
| N0 | 49 (34.5) |
| N1 | 65 (45.8) |
| N2 | 3 (2.1) |
| Unknown | 25 (17.6) |
| Neoadjuvant treatment | |
| Neoadjuvant treatment | 88 (62) |
| No neoadjuvant treatment | 52 (36.6) |
| Unknown | 2 (1.4) |
| Response to neoadjuvant treatment | |
| No residual tumor (complete response) | 17 (12) |
| Residual tumor present (partial response) | 71 (50) |
| No neoadjuvant treatment | 52 (36.6) |
| Unknown | 2 (1.4) |
| Tumor grade | |
| Well differentiated | 4 (2.8) |
| Moderately differentiated | 67 (47.2) |
| Poorly differentiated | 61 (43) |
| Unknown | 10 (7) |
| Disease relapse | |
| Yes | 43 (30.3) |
| No | 91 (64.1) |
| Unknown | 8 (5.6) |

GIST: Gastrointestinal stromal tumor.

Table 2 First site of esophageal cancer relapse following esophagectomy

| Relapse site | $n$ (%) |
|-------------|---------|
| Brain | 9 (21) |
| Peritoneum | 3 (7) |
| Esophageal remnants, paraesophageal lymph nodes or mediastinum (locoregional relapse) | 13 (30) |
| Lungs | 8 (19) |
| Liver | 6 (14) |
| Bone | 4 (9) |
DISCUSSION

Esophageal cancer is potentially a curable disease if diagnosed at an early stage but fatal when widely metastatic. The current standard of care of locally advanced esophageal cancer includes neoadjuvant concurrent chemotherapy and radiation therapy followed by esophagectomy\(^{[9,20]}\). Although significant advances have been made in achieving better quality of life and survival outcomes, it is estimated that only around 20% of the patients with local disease are alive 5 years following diagnosis\(^{[21,22]}\).

Brain metastasis as the first site of disease relapse after esophagectomy for esophageal cancer is uncommon\(^{[3,4]}\). However, our study showed a higher frequency of brain relapses in locally advanced esophageal cancer patients who underwent esophagectomy compared to historical figures\(^{[3]}\). Recognizing the increased risk of brain metastasis in HER-2 positive breast cancer patients\(^{[13,14]}\) and the known overexpression of HER-2 in esophageal cancers\(^{[25,26]}\), we explored HER-2 expression status in the brain metastasis tissues obtained from esophageal cancer patients who underwent esophagectomy and relapsed in the brain. HER-2 was strongly positive in 50% of the cases which probably implies that HER-2 positivity in esophageal cancer predisposes to brain metastasis. Interestingly, in a phase I/II trial by Safran et al\(^{[23]}\) testing Trastuzumab in HER-2 positive esophageal cancer patients, 3 out of the 10 relapses that occurred were in the central nervous systems (CNS).

Treatment of CNS metastasis, regardless of the primary cancer type, often includes surgery, radiation therapy or chemotherapy. Although surgical resection or SRS of a limited number of brain metastasis resulted in survival benefit in various cancers including esophageal cancer\(^{[26-28]}\), chemotherapy treatment of CNS metastasis has been limited, primarily due to the blood brain barrier in addition to other factors\(^{[29,30]}\). Nevertheless, there have been recent advances in the chemotherapeutic management of CNS metastasis, whether parenchymal or leptomeningeal. Whereas Trastuzumab is known to be an effective treatment of metastatic HER-2 positive breast cancers, its CSF levels were reported to be low when administered intravenously\(^{[31]}\). Alternatively, intrathecal Trastuzumab showed encouraging results treating HER-2 positive breast cancer leptomeningeal metastasis\(^{[32,33]}\). Lapatinib, an oral HER-2 tyrosine kinase inhibitor that crosses the blood brain barrier, combined with Capecitabine resulted in partial and complete responses of brain metastasis from HER-2 positive breast cancers\(^{[34-37]}\).

In summary, we noticed a high incidence of brain metastasis as the first site of cancer relapse in our series of locally advanced esophageal cancer patients who underwent esophagectomy. Additionally, we observed that HER-2 overexpression might be associated with increased risk of brain metastasis. The benefits of screening brain imaging in a selected population of HER-2 positive esophageal cancer patients before going through a major surgery such as esophagectomy and utilizing HER-2 directed therapy in case of brain relapse in that same subpopulation are potential considerations that deserve further exploration in future studies. Acknowledging the limitations of a retrospective study and the small sample size, our observations need to be replicated in a larger cohort.
Applications
If subsequent larger studies support our observation of increasing risk of brain relapse from HER-2 overexpressing esophageal cancer, this will have various important implications. This subset of patients might benefit from screening brain imaging to rule out brain metastasis. This might decrease the number of futile esophagectomies which will be avoided if the patient is found to have brain metastasis before surgery. Additionally, there might be a role for biological agents, such as Trastuzumab or Lapatinib in the treatment of brain relapse from HER-2 overexpressing esophageal cancers.

Terminology
HER-2 is a membrane tyrosine kinase involved in signal transduction pathways that regulate cellular proliferation. Overexpression of HER-2 was identified in various cancers, such as esophageal, gastric and breast cancers. It correlates with an aggressive disease and worse prognosis in breast cancer. Antibodies that target HER-2, such as Trastuzumab, are available for clinical use and commonly utilized in breast cancer. Trastuzumab was also found to prolong survival in women with HER-2-positive breast cancer by reducing the risk of death compared to chemotherapy alone by 30%. Antibodies that target HER-2, such as Trastuzumab, are available for clinical use and commonly utilized in breast cancer. Trastuzumab was also found to prolong survival in women with HER-2-positive breast cancer by reducing the risk of death compared to chemotherapy alone by 30%.

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Peer review
This paper presents an interesting topic about the relationship between HER-2 OVER expression and brain metastasis in esophageal cancer patients.

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