Oligometastatic Adenocarcinoma of the Esophagus

Subjects: Oncology

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Esophageal adenocarcinoma is an aggressive cancer of increasing incidence and is associated with poor prognosis. The early recognition of synchronous and metachronous oligometastasis in esophageal adenocarcinoma may allow for prompt intervention and potentially improved survival. However, curative approaches to oligometastatic esophageal disease remain unproven and may represent an area of emerging divergence of opinion for surgical and medical oncologists. We sought to identify the current understanding and evidence for management of oligometastatic esophageal adenocarcinoma by performing a thorough review of the available literature

Keywords: esophageal adenocarcinoma ; esophageal cancer ; oligometastasis

1. Introduction

Esophageal adenocarcinoma (EA) comprises up to 80% of esophageal cancer in the United States and is a major cause of cancer morbidity and mortality worldwide [1]. While esophageal squamous cell carcinoma has been declining in the United States and in other parts of the western world, EA incidence has experienced a five-fold increase over the last four decades [2]. The five-year overall survival rate from 2009–2015 was 19.9%, with patients without lymph node involvement experiencing significantly better prognosis than those with involved lymph nodes [3]. Although surgical resection remains the mainstay treatment, survival is poor due to the high incidence of locoregional or distant metastasis [4][5][6]. Accordingly, a multimodal approach of neoadjuvant chemoradiotherapy (i.e., cT1b-T4a, N0-N+ staged patients) or perioperative chemotherapy alone (i.e., cT4b staged patients) has become the standard of care [7][8]. While oncologic outcomes have improved with multimodal therapy, five-year survival rates continue to give cancer specialists pause. This poor prognosis has highlighted the need for refinements in current treatment practices and pursuits of novel understandings in tumor biology, microenvironment, invasion tactics, and metastatic potential. The early identification and treatment of oligometastatic esophageal adenocarcinoma represents one such strategy.

Though no exact definition exists, oligometastatic disease is generally characterized by a state of limited metastatic burden of less than five metastases, and can be detected at the time of primary cancer diagnosis, so-called synchronous oligometastasis, or detected following treatment of the primary tumor, known as metachronous oligometastasis [9][10]. Whether this state represents an intermediate step in widespread metastasis or is a distinct molecular metastatic pattern remains debatable [11]. Regardless, the potential for improved survival outcomes with early detection, and thus earlier treatment, is of significant interest. Metastatic esophageal disease is largely regarded as an end-stage condition, with many patients offered palliative therapy. Consequently, the ability to detect and intervene prior to widespread metastatic burden remains a topic of significant research. Currently, no consensus treatment guidelines exist for oligometastatic esophageal cancer, mainly due to the paucity of large randomized control trial data in this cohort. We sought to identify the current understanding, diagnostic tools, and treatment modalities available in oligometastatic esophageal adenocarcinoma by performing a thorough review of the available literature.

2. Molecular Mechanisms

Important insights have been made into the molecular underpinnings of esophageal adenocarcinoma and their role in oligometastatic and widely metastatic disease. Various studies have identified potential mechanisms contributing to increased tumor size, invasion, and metastasis. These pathways have improved the understanding of esophageal carcinoma and identified potential novel therapeutic targets. Although the precise molecular mechanisms contributing to oligometastatic disease remains elusive, several potential contributors of invasion and metastatic spread have been identified and are the focus of ongoing investigations.

Somatic point mutations in the tumor suppressor TP53 (responsible for p53 protein production) represent the most frequent gene mutations occurring in approximately 50% of esophageal carcinomas [12]. Efforts at exome and whole-genome sequencing have identified a high frequency of mutations in esophageal carcinoma, outpaced by only melanoma

and lung cancer [12][13]. Other significantly altered genes, including p16/CDKN2A, ELMO1, DOCK2, ARID1A, SMARCA4, and ARID2, have been implicated in metastatic potential through various mechanisms [12].

Wang et al. recognized increased lymph node metastases in esophageal adenocarcinoma specimens that over-expressed Dickkopf-3 (DKK3) [14]. A member of the Wnt inhibitor family, evidence suggests DKK3 may act as a tumor suppressor in the metastatic setting in some cancers and is over-expressed, leading to cancer invasion, angiogenesis, and chemoresistance in others. DKK3 has been hypothesized to regulate FGF and Activin/Nodal via SMAD4 and influence the TGF-β pathway. The authors demonstrated significant over-expression of DKK3 in esophageal adenocarcinoma, promoting increased proliferation, invasion, and chemoresistance, and they suggested it may play an important role in tumor growth and metastatic disease [14]. Toll-like receptor 5 (TLR5) and tumor-associated glycoprotein 72 (TAG-72) have also been implicated in lymph node metastases [15][16]. Xu et al. found TAG-72 levels significantly correlated with lymph node status and the extent of invaded lymph nodes, suggesting its use as a potential future clinical predictor [16]. TLR5 has been proposed to activate nuclear factor-κB (NF-κB) in gastric cancer [17][18]. Suppression of NF-κB in gastroesophageal junction carcinoma cell lines leads to a blockade of metastasis, and is thus felt to be implicated in metastatic potential when activated [17].

IGF2 mRNA binding protein 2 (IGF2BP2/IMP2) was originally identified as an autoantigen in hepatocellular carcinoma but has also recently been implicated in esophageal adenocarcinoma [19]. Barghash et al. demonstrated esophageal adenocarcinoma, and Barrett's esophagus tissue showed over-expression of IMP2, particularly in those of increased size and in metastatic tissue. IMP2 is involved in cell metabolism and high expression correlated with growth, proliferation, metabolism, inflammation, and cancerous processes [19]. IMP2 expression leads to elevated levels of IGF2, which may activate MAPK and Jak-STAT signaling pathways and is associated with poor prognosis in esophageal carcinoma [17].

Various single case reports of alpha-fetoprotein (AFP) producing esophageal adenocarcinomas leading to liver metastases are described in the literature, but have not been described in large cohorts [20][21][22]. Aside from the aforementioned contributors to lymph node metastases and sporadic case reports, existing literature is sparse concerning the precise underlying mechanisms contributing to oligometastatic disease.

While the complete cadre of contributing molecular factors has yet to be elucidated, important inroads into understanding these processes has been made. As additional investigations continue to improve our understanding of the genes and molecular mechanisms involved in oligometastatic EA, targeted therapies may improve the relatively discouraging five-year survival rates currently experienced.

3. Current Management

Current treatment strategies in the United States for esophageal adenocarcinoma rely on the recommendations of the National Comprehensive Cancer Network (NCCN, Plymouth Meeting, PA, USA) guidelines and are generally based on a multidisciplinary team approach tailored to the individual patient's American Joint Committee on Cancer (AJCC, Chicago, IL, USA) stage, Siewert–Stein classification, co-morbidities, and other factors [23]. In patients with locally advanced (T3-T4) or cN1-N3 (lymph node metastasis according to clinical evaluation) esophageal tumors, neoadjuvant chemotherapy or chemoradiotherapy plus resection is required, with most centers tailoring this approach based on histologic subtype [7][24][25]. Traditional dogma and guidelines recommend against attempted curative resection and metastasectomy in patients with cancers that are felt to be unresectable, or in those with distant disease (T4b, any N, or M1), with instead a focus on palliative chemoradiotherapy [25][26]. However, contemporary literature has somewhat challenged this philosophy. The recent results of the multicenter German AIO-FLOT3 and AIO-FLOT4 studies evaluating locally advanced, resectable tumors of the esophagogastric junction (EGJ) and stomach suggests well-selected patients may benefit from surgery and peri-operative chemotherapy, and indeed has provided rational for further randomized clinical trials in this cohort [27][28]. These included patients with histologically confirmed, previously untreated, nonmetastatic, operable (>T2, N any, and M0 or any T, N+, and M0), or metastatic (T any, N any, and M1) adenocarcinoma of the stomach or gastroesophageal junction without disease recurrence or uncontrolled medical illness, and with sufficient bone marrow and kidney function [27]. Additional investigations from subgroup analyses of clinical trials, retrospective patient cohorts, the Japan Clinical Oncology Study, and current RENAISSANCE (AIO-FLOT5) trial also highlight the ongoing debate of surgical intervention in limited metastatic gastric and esophagogastric cancers [29][30].

4. Conclusions

The support of surgical intervention in oligometastatic esophageal adenocarcinoma has continued to gain favor over the last decade in carefully selected patients [27][31][32][33][34][35][36][37][38][39]. Emerging randomized trial evidence is set to define

this role and quantify the potential benefit of surgical resection, or lack thereof. Important innovations in chemotherapeutics and targeted therapies are currently reimagining treatment paradigms. The importance of an experienced multidisciplinary team approach and tailored treatment strategy cannot be understated. Overall, patient selection remains paramount to ensuring optimal outcomes and should include consideration for resectability of the primary tumor and metastases, general patient condition, and response to chemotherapy.

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