Modern Oncological Approaches to Gastric Adenocarcinoma

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KEYWORDS

• Gastric cancer • Gastric adenocarcinoma • Multidisciplinary approach
• Perioperative • Chemoradiation • Adjuvant therapy

KEY POINTS

- Gastric cancer (GC) is the fourth most common cancer in men and the fifth most common cancer in women worldwide.
- Surgery is the key for curing patients with localized GC. However, surgery alone is insufficient to achieve the highest possible cure rate, which can be obtained by the addition of adjunctive therapies.
- Advanced GC is an incurable condition; however, it is now possible to prolong survival with oncologic therapies.
- Patients with advanced GC with Her2-neu protein overexpression can benefit from the addition of trastuzumab to combination chemotherapy.
- Improved therapy will likely result from a better understanding of the molecular pathways in GC.

INTRODUCTION

GC is frequently diagnosed in the advanced stage and is associated with a poor prognosis. The incidence of GC still remains high, and there are many endemic areas in the world. Annually, the estimated number of new GC cases worldwide is 640,600 for men and 349,000 for women.[1] In 2012, approximately 21,320 new cases were likely to be diagnosed and 10,540 patients were expected to die in the United

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States.[2] Localized GC (LGC) is a potentially curable condition, and surgery plays a major role in the achievement of cure. The cure rates from surgery vary considerably with regions but are predominantly based on the surgical stage of LGC; however, surgical technique and surgical volume (of a center and surgeon) highly contribute to the cure rates (as well as the rates of complications and mortality). Advanced GC (AGC) is a treatable but not curable condition. AGC and LGC are highly heterogeneous (driven by patient and tumor genetic differences). In this regard, discovery of tumor subsets defined by their molecular subtypes (eg, Her2-neu overexpressing tumors vs those that do not overexpress Her2-neu) is likely to drive the direction of future research and to set the stage for improved and individualized therapies. This review highlights the current therapeutic strategies for LGC and AGC.

LOCALIZED GASTRIC CANCER (LGC)

Baseline clinical stage should be established meticulously.[3] Although baseline clinical stage is not as highly associated with long-term outcome as the surgical pathology stage,[4] the baseline clinical stage does help to define the short-term therapeutic strategy. It is important to emphasize that physician(s) from one discipline (eg, a gastroenterologist or a surgeon) should not decide the initial therapeutic strategy of LGC but that a consensus decision, derived from a multidisciplinary discussion of the baseline staging of patients with LGC, should be reached because this is likely to provide the highest benefit to a patient.[3,5]

Once it is established that the patient has LGC, the therapeutic plan should include adjunctive strategy for most patients (an example of an exception would be an LGC <3 cm in diameter and $\leq$T1bN0). The preferred adjunctive strategy differs by region worldwide, reflecting differences in practice patterns. The extent of lymphadenopathy also varies, and it is usually suboptimal in most areas of the world where GC is not highly prevalent. Surgery remains the best contributor to the cure rate, and when surgery is not done or not possible, one can anticipate a dismal outcome.[6] In the following section we discuss adjunctive strategies.

ADJUNCTIVE STRATEGIES

Postoperative Adjuvant Chemoradiation

The most important study that established this strategy firmly in the West is the Intergroup 0116 trial, headed by the Southwest Oncology Group.[7] This trial was based on prior nonrandomized observations in patients with LGC who received chemoradiation therapy. This trial was a phase 3 study that compared observation after surgery (control) with chemoradiation adjuvant after following surgery (experimental arm).[7]

Three other relevant studies are worth mentioning. The CALGB-driven intergroup adjuvant trial did not take advantage of improving chemoradiation efforts and instead compared fluorouracil to the combination of epirubicin/cisplatin/fluorouracil and demonstrated no advantage with the latter.[9] The second study was a retrospective comparison of 2 patient populations (one group had surgery and the other had surgery plus chemoradiation), and this comparison demonstrated benefit for the chemoradiation group.[10] However, the use of a retrospective design greatly limits this conclusion. The third study was a prospective comparison in patients with LGC who had an excellent D2 dissection (median number of nodes evaluated was >30). In this ARTIST trial (Adjuvant Chemoradiation Therapy in Stomach Cancer), both group of patients were treated after surgery (chemotherapy vs chemoradiation).[11] The primary analysis of