Editorial

Duodenal adenocarcinoma: more questions than answers

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Duodenal adenocarcinoma (DA) is an aggressive malignancy. It represents the most common adenocarcinoma of the small intestine, with the majority arising in segment D2 (1-3). The incidence of DA however is rare; it represents less than 1% of all gastrointestinal cancers (4-6). DA usually presents with vague symptoms and can be difficult to diagnose until a patient develops gastrointestinal bleeding or obstruction which frequently results in delays of diagnosis (7). These factors influence the lack of high-quality evidence on outcomes for those with DA, relative scarcity of definitive treatment recommendations, and resulting overall modest prognosis.

In a recent issue of the *Annals of Surgical Oncology*, Meijer *et al.* present a systematic review and meta-analysis on the long-term outcomes and prognostic factors of DA. Prior research on DA has been limited by small sample sizes and single institutional design. Here, in rigorous fashion and with proper statistical methods, the authors utilized the data of 6,438 patients with DA extracted from 26 observational studies to illustrate patient outcomes for (neo)adjuvant therapy, surgery, and palliative measures.

Their analysis confirms existing principles on factors influencing the prognosis of patients with DA. First, complete surgical resection is the only chance at cure (3). From the pooled data, the authors demonstrate 5-year survival rates of 46% for those who underwent curative resection (when curative intent was feasible), compared to only 1% for those patients who underwent palliative resections. Even after acknowledging that the palliative group surely represents patients with greater burden of disease, this significant difference in long-term survival highlights the reality that the prognosis of patients with unresectable DA is very poor, with complete resection offering substantial benefit.

Second, their findings re-emphasize the need for sampling lymph nodes through formal lymphadenectomy, which rids existent disease and provides valuable prognostic information. Indeed, the pooled 5-year survival rate was 65% for node negative disease compared with 21% for node positive disease. Although most clinicians agree on the need to ensure wide margins and adequate regional lymphadenectomy, a debate persists over the optimal surgical approach. One group believes pancreatoduodenectomy should be performed for all DA, regardless of location, in order to provide adequate lymph node sampling (8-10). Others argue that for DA located in the very proximal or distal duodenum, one can achieve sufficiently wide margins with a segmental resection, negating a need to always perform a pancreatoduodenectomy, and thus avoiding the complications and life-style adjustments associated with this procedure (11). Meijer *et al.* re-affirm that there is no difference in survival between these surgical approaches, providing us with further evidence that either surgical approach is acceptable as long as negative margins are achieved and an adequate lymphadenectomy is performed.

Perhaps the real value hidden in Meijer and colleagues' report is that it highlights the obvious shortcomings in current literature regarding recommendations for (neo) adjuvant therapies for DA. First, there is no evidence-based protocol for adjuvant therapy with a variety of practices being performed. Meijer et al included data from six studies that investigated 5-year overall survival for any type of adjuvant therapy compared with no adjuvant therapy, and

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found no significant differences in outcomes between groups (12). This likely highlights the lack in quality of existing data rather than a declaration that there is no role for adjuvant therapy for patients with DA. As the incidence of DA is rare, generating level 1 evidence on optimal adjuvant therapy with randomized controlled trials will be extraordinarily challenging, however not impossible. The ESPAC-3 trial was a phase 3, multi-institutional, randomized controlled trial comparing observation vs adjuvant fluorouracil vs adjuvant gemcitabine in patients with periampullary cancers (2.3% DA) who underwent pancreatoduodenectomy with R0 or R1 resection status. Therein, adjuvant chemotherapy was associated with improved overall survival during multivariable regression analysis (hazard ratio =0.75, 95% confidence interval: 0.57–0.98) (13). Although recruitment for DA could have been improved, it highlights the need for multi-institutional collaboration and innovative ways to gain insight into future treatments. Of note, while the role of adjuvant therapy warrants further investigation, given the lack of evidence to guide specific chemotherapy regimens, most clinicians use similar regimens to that used for colorectal cancer (e.g., oxaliplatin-based) (3,14).

Still more lacking is evidence for neoadjuvant therapy. Meijer *et al.* report on five studies comprising a total of 117 patients who underwent preoperative chemotherapy and/or radiotherapy without measurable benefit or survival impact (12). Despite their findings, emerging evidence tends to suggest that some patients with DA respond to neoadjuvant therapy and this may hold vital prognostic information (15). Neoadjuvant therapy is increasingly being performed for other periampullary cancers and further investigation into the role for neoadjuvant therapy is needed for DA, especially among patients with clinically node positive or large tumors (16,17).

DA is a rare but aggressive malignancy for which a paucity of existing data still complicates our understanding of appropriate treatment strategies. The recent meta-analysis and systematic review by Meijer *et al.* is a welcome addition to the literature on DA by pooling currently available data to clarify prognosis, confirming the importance of surgical resection, and reminding of the need for well-designed prospective clinical trials. Further rigorous investigation, with special attention to multi-institutional trials looking at tumor biology-related factors, subgroup analyses, and targeted approaches, are needed in effort to formulate high-level, evidence-based treatment algorithms to improve patient outcomes. In the meantime, lessons learned from other periampullary cancers should still be applied to this rare malignancy.

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