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EDITORIAL – PANCREATIC TUMORS

Is Margin Status Less Prognostic After Neoadjuvant Chemoradiotherapy for Pancreatic Adenocarcinoma?

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Margin status is an independent risk factor for survival of patients undergoing surgery for pancreatic adenocarcinoma[1]. A number of different strategies are aimed at decreasing the risk of a positive surgical margin (R1 and R2). These strategies include accurate staging,[2] excellent surgical technique,[3] artery-first approaches to dissection,[4] radical resections including arterial and multi-visceral resections,[5] stereotactic radiation therapy and dose-escalation techniques, irreversible electroporation, and neoadjuvant chemotherapy with or without radiotherapy therapy.[6] All these strategies are aimed at decreasing the risk of residual locoregional disease except neoadjuvant chemotherapy, which also aims at decreasing the risk of systemic disease.

Neoadjuvant treatment has become the standard of care for many cancers, but for pancreatic cancer, the adoption has been slower. For this cancer, it was introduced to treat a subset of patients with anatomically aggressive features, those defined as borderline resectable,[7] to reduce the risk of a positive margin and residual disease.

The numerous advantages of neoadjuvant therapy have currently been largely accepted. It offers early treatment of undetected microscopic systemic disease, ensures that all eligible patients are treated, allows the imminent development of metastases to be detected before patients undergo futile surgery, provides the opportunity for downstaging, decreases the rate of clinically relevant postoperative fistula, and increases the negative margin (RO) rate. Because it makes little sense to reserve these advantages for patients with borderline resectable disease, there has been a notable pivot toward offering it to patients with resectable disease as well.[7] Despite these advantages, some patients and surgeons retain a preference for "surgery-first," being reluctant to delay resection for the sake of neoadjuvant therapy.

The single-center study by Zhang et al.[8] in this issue of *Annals of Surgical Oncology* examines the prognostic significance of surgical margin status in two groups of patients who had resection of pancreatic adenocarcinoma: those who had neoadjuvant chemoradiotherapy (NACRT) and those who had upfront surgery with adjuvant chemoradiotherapy (ACRT). The primary aim of this study was to determine whether the prognostic significance of a positive surgical margin status was similar between these two groups.

The authors report that patients with a positive margin after NACRT plus surgery had a significantly longer median survival than those with a positive margin after upfront surgery plus ACRT. Although the overall median survival in the NACRT group was longer, a notable finding in the multivariable analysis showed that surgical margin status did not influence survival in the NACRT group but did have an impact on survival in the ACRT group. Although this difference was significant, it is worth noting that the overall survival curves of these two groups converged approximately 90 months after treatment.

The study also confirmed that a "close" surgical margin (<1 mm) had the same prognostic significance as a positive margin and that NACRT was associated with more peri-

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tumoral fibrosis, more negative lymph nodes, and less perineural invasion. The authors concluded that NACRT should be strongly considered for patients at high risk for an R1 resection, and they highlighted a number of open phase 2 and 3 studies examining just that. The authors made excellent use of their dataset and provided further evidence to support neoadjuvant treatment for patients at risk of incomplete resection.

Although the aforementioned stance has been widely accepted, some caution is advised in relation to this particular study. This caution is advised because a definitive comparison of the prognostic significance of margin status between these two patient groups is impossible (and acknowledged) because control was not used for other prognostic factors in this non-randomized retrospective study, which was prone to selection bias.

The comparison, despite the sensitivity analyses, offers no more than an association between margin status and survival because of the differences (both stated and anticipated) between the groups in terms of age, pretreatment staging and involvement of vessels, patient performance status and comorbidities, heterogeneity of pancreatic cancers and actionable subtypes, histologic differentiation and biologic aggressiveness, types of pancreatic resections, consistency and radicality of pancreatoduodenectomy, neoadjuvant and adjuvant treatment protocols, referral patterns over time, and completion rates of treatments.

The comparison also showed evidence of cross-contamination, with about 8 % of the NACRT group receiving prior induction chemotherapy and 54 % receiving adjuvant chemotherapy. The ARCT group also had a notable variation, with only 72 % receiving adjuvant chemotherapy and 65 % receiving adjuvant radiotherapy.

Another retrospective study from three centers (USA and Japan) using more contemporary and varying neoadjuvant chemotherapy as well as chemoradiotherapy regimens for both resectable and borderline resectable disease in patients who had a pancreatoduodenectomy found a similar relationship between survival and margin status in a multivariate Cox regression analysis.[9] An R1 resection was independently associated with poor overall survival after surgery (hazard ratio, 4.74; 95 % confidence interval, 2.24–9.46). The study showed other significant predictors of overall survival including histologic grade, treatment effect, postoperative carbohydrate antigen 19-9 (CA19-9), and receipt of adjuvant treatment. These findings are consistent with a growing body of evidence that supports NACRT becoming the standard of care for all patients with resectable and borderline resectable pancreatic adenocarcinoma.

As with all valuable studies, this study by Zhang et al.[8] highlights some important unresolved issues. The first is whether NACRT has a continuing effect beyond resection and whether some reported positive margins might have become negative with more time. The contribution of radiotherapy to chemotherapy in relation to the observed effect is not known, especially in the context of contemporary and more effective chemotherapy options (including FORFIRINOX and nab-paclitaxel) as well as emerging personalized strategies.[10]

The optimal protocol for radiotherapy remains to be defined, and it is not known whether it should be offered to only those with a confirmed positive margin. New approaches to re-staging and assessment of residual tumor after NACRT are needed[11] because of the difficulty distinguishing the effect of treatment from tumor extension, desmoplasia, and inflammation.

The prognostic significance of a positive margin appears to be less important after NACRT, but this should not be taken as a reason to not continuing to strive to achieve complete resection through excellent surgery. Many questions remain about the makeup and timing of neoadjuvant therapy, and the need for well-powered multi-center prospective randomized studies has never been greater. This is crucial to reap the benefits of NACRT, not only with regard to margin status but also due to increasing the chance of long-term survival.

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