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Circulating tumor DNA (ctDNA) monitoring for minimal residual disease (MRD) in gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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BACKGROUND

GEP-NETs present unique challenges in post-surgical surveillance due to variable disease behavior and limited predictive biomarkers. ctDNA has emerged as a promising tool MRD detection in other gastrointestinal malignancies. However, ctDNA shedding in NETs is generally lower and more variable compared to adenocarcinoma. This study investigated the feasibility of post-operative ctDNA testing in GEP-NET.

METHODS

We conducted a retrospective analysis of 40 patients who underwent curative intent surgery for GEP-NET with at least one post-operative ctDNA sample. Demographic and baseline characteristics were summarized using descriptive statistics. Event time distributions were estimated using Kaplan-Meier methods with confidence intervals calculated using Brookmeyer and Crowley methodology. Median follow-up was reported using the reverse Kaplan-Meier method. The association between longitudinal ctDNA positivity and disease-free survival was assessed using a Cox regression model with a time-dependent covariate for first occurrence of a positive ctDNA test.

RESULTS

ctDNA testing was successful in 39 of 40 patients (97.5%). Primary sites of disease included pancreas (48%), small bowel (35%), ampullary (5%), appendiceal (5%), colon (5%), and gallbladder (2%) NETs. Median follow-up was 39.7 months (95% CI: 23.7, 48.4). The median number of post-operative ctDNA samples was 6 (range: 1-15). Eight of 39 patients had positive ctDNA, and all eight experienced recurrence resulting in a positive predictive value of 100% (95% CI 63, 100). Three additional recurrences were observed without detectable ctDNA, yielding a sensitivity of 73% (95% CI 39, 94). ctDNA was negative in 31 patients, with a negative predictive value of 90% (95% CI: 74, 98). Median time from first

positive ctDNA to radiographic recurrence detection was 152 days (range: -17, 1022). ctDNA positivity was associated with higher grade tumors, higher Ki-67, and perineural invasion. Time-dependent covariate analysis demonstrated that becoming ctDNA positive following surgery significantly increased the risk of progression or death (HR=33.7; 95% CI: 6.9, 164.8; p<0.0001).

CONCLUSIONS

Post-operative ctDNA testing is feasible in GEP-NET patients following curative intent surgery. All ctDNA-positive patients experienced disease recurrence, and ctDNA positivity preceded radiographic detection in most patients. These retrospective findings support ctDNA monitoring as an emerging valuable surveillance tool in GEP-NET and warrants continued investigation.

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