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Original article

Mitotic index and multipolar mitosis in routine histologic sections as prognostic markers of pancreatic cancers: A clinicopathological study

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ABSTRACT

Objectives: Pancreatic cancer is characterized by genomic complexity and chromosomal instability, and atypical mitotic figures are morphological features of this phenotype. In the present study, we determined the frequency and the clinicopathological and prognostic significance of mitotic figures in pancreatic cancers.
Methods: We surveyed the mitotic figures of the normal ductal epithelium, acinar cells, pancreatic intraepithelial neoplasias, and pancreatic cancers on hematoxylin-and-eosin–stained tissue specimens (n = 121).
Results: Pancreatic cancer cells showed significantly higher mitotic indices as compared with the ductal cells, acinar cells, and pancreatic intraepithelial neoplasias. Both normal and atypical mitosis were significantly elevated only in pancreatic cancers. In pancreatic cancers, approximately 30% of total mitosis was atypical including multipolar, lag-type, ring and asymmetrical mitosis, and anaphase bridges. The Kaplan–Meier curves in pancreatic cancers showed significant correlations between total mitosis and disease free survival. Furthermore, the cases with multipolar mitosis showed poorer prognosis than those without. Lymph node metastasis and multipolar mitosis were independent prognostic factors for overall survival of patients with pancreatic cancer. In addition, lymph node metastasis and total mitosis were independent factors for disease free survival.
Conclusion: These findings suggest that routinely obtained pathological specimens, even small biopsy or cytological specimens, can provide valuable information concerning the prognosis of pancreatic cancers.

Introduction

Some of the important indicators of prognosis after pancreatic cancer resection are lymph node metastasis status [1], tumor stage [2], and resection margins [3]. The histologic grade, based on multiple parameters including differentiation status, mucin production, mitotic counts, and nuclear polymorphism, has been reported as an independent prognostic marker superior to the immunohistochemical assessment of proliferation [4]. Patterns of infiltration, similar to Gleason's scoring system, have also been reported as independent prognostic markers for pancreatic cancer [5].

Pancreatic cancer is characterized by genomic complexity and chromosomal instability; telomere dysfunction, aneuploidy, polyploidy, nuclear atypia, and abnormal mitosis are all contributors to this phenotype [6–9]. Previously, we showed that the age-related

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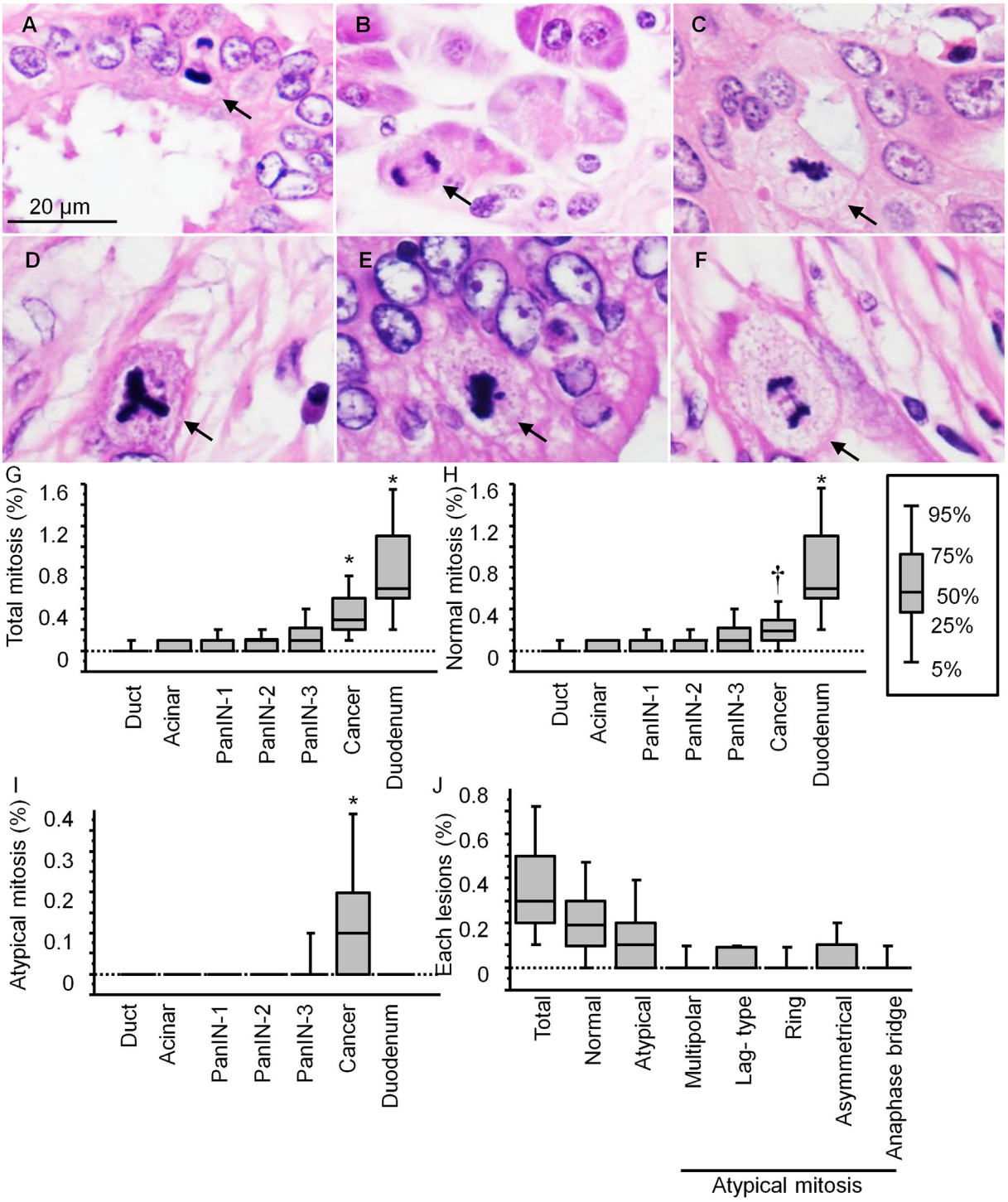

Fig. 1. Mitotic figures in pancreatic tissue. Normal mitosis in the pancreatic duct (A), acinar cells (B), and cancer (C), in metaphase (A and C) and anaphase (B). Atypical mitosis in pancreatic cancer (D–F). Multipolar mitosis (D), lag-type mitosis (E), and anaphase bridge (F). Percentage of total mitosis (G), normal mitosis (H), and atypical mitosis (I) in each tissue type. *; $P < 0.05$ vs. others. †; $P < 0.05$ vs. duct, acinar cells, and PanIN-1. (J) Percentage of each mitotic figure in pancreatic cancer cells.

shortening of telomere length in normal pancreatic tissue was 36 base pairs per year [10]. Telomere dysfunction induces fusion of chromatids and chromosome missegregation, and this phenomenon can be observed as an anaphase bridge, a type of abnormal mitotic figure [11–13]. We found that the telomere length of pancreatic cancers negatively correlated with the incidence of abnormal mitotic figures—including anaphase bridges [14]—suggesting that abnormal mitosis is a useful marker for chromosomal instability due to telomere dysfunction. A previous report has shown that single nucleotide polymorphisms in regulators of mitosis may promote chromosome missegregation and influence the predisposition to pancreatic cancers and survival [15]. These data indicate that mitotic figures, which are easily assessed using routine pathological specimens, can provide important information