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REVIEW

Treatment for superficial non-ampullary duodenal epithelial tumors

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Abstract

Because of the low prevalence of non-ampullary duodenal epithelial tumors (NADETs), standardized clinical management of sporadic superficial NADETs, including diagnosis, treatment, and follow-up, has not yet been established. Retrospective studies have revealed certain endoscopic findings suggestive of malignancy. Duodenal adenoma with high-grade dysplasia and mucosal cancer are candidates for local resection by endoscopic or minimally invasive surgery. The use of endoscopic treatment including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), for the treatment for superficial NADETs is increasing. EMR requires multiple sessions to achieve complete remission and repetitive endoscopy is needed after resection. ESD provides an excellent complete resection rate, however it remains a challenging method, considering the high risk of intraoperative or delayed perforation. Minimally invasive surgery such as wedge resection and pancreas-sparing duodenectomy are beneficial for superficial NADETs that are technically difficult to remove by endoscopic treatment. Pancreaticoduodenectomy remains a standard surgical procedure for treatment of duodenal cancer with submucosal invasion, which presents a risk of lymph node metastasis. Endoscopic or surgical treatment outcomes of superficial NADETs without submucosal invasion are satisfactory. Establishing an endoscopic diagnostic tool to differentiate superficial NADETs between adenoma and cancer as well as between mucosal and submucosal cancer is required to select the most appropriate treatment.

Key words: Duodenal neoplasms; Duodenal cancer; Pancreaticoduodenectomy; Endoscopic surgery; Esophagogastroduodenoscopy

Core tip: Superficial non-ampullary duodenal epithelial tumors (NADETs) including adenoma and mucosal cancer are candidates for local resection regarding the nil risk of lymph node metastasis. Pancreaticoduodenectomy remains a standard surgical procedure for treatment of duodenal cancer with submucosal invasion. Preoperative diagnosis to differentiate superficial NADETs between adenoma and cancer as well as between mucosal and submucosal cancer is essential to select minimally invasive treatment such as endoscopic resection or minimally invasive surgery.

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INTRODUCTION

The prevalence of non-ampullary primary duodenal tumors is extremely low among autopsy studies (0.02%-0.5%)[1-4]. Benign tumors are generally predominant, comprising 60%-75% of autopsy series[5], and 90% of duodenal polyps identified by endoscopic biopsy[6], but they frequently do not produce symptoms. Primary non-ampullary duodenal cancer (NADC) accounts for only 0.5% of all gastrointestinal malignancies[7]. A Japanese study reported that the incidence of non-ampullary duodenal epithelial tumors (NADETs) among patients who underwent screening or diagnostic esophagogastroduodenoscopy (EGD) over a 21-year period was 0.098% (52/53134)[8]. A European study reported that the incidence of duodenal villous adenoma was 0.1%-0.4%[9,10] among patients who underwent diagnostic or screening EGD.

The number of case studies related to the treatment of sporadic superficial NADETs has recently increased, possibly because of the use of EGD during regular medical check-ups and the standardized method of imaging the second portion of the duodenum during EGD. However, information regarding the biological behavior, treatment indication, and prognosis of NADETs is still lacking. In this review, the present status regarding the clinical management of sporadic superficial NADETs will be discussed.

MORPHOLOGY OF NADETs

The morphology of superficial NADETs is similar to that of epithelial tumors of the colorectum; protruding or elevated lesion types predominate. Therefore, several previous studies have classified the morphological type of superficial NADETs based on the classification criteria used for colorectal tumors[11-13]. Macroscopic types based on endoscopic features include protruded pedunculated (Ip), protruded sessile (Is), semipedunculated type (Isp), superficial elevated type (Ⅱa), flat type (Ⅱb), and superficial shallow or depressed type (Ⅱc)[14].

LOCATION OF NADETs

Both benign adenoma and cancer arise most frequently in the second portion of the duodenum, especially the periampullary area[15-17]. Almost 90% of endoscopically treated lesions are reportedly located in the first or second portion of the duodenum[11,12]. However, an accurate prognosis according to the location remains unknown for superficial NADETs, although tumors in the first or second portion are reportedly favorable factors for surgically treatable duodenal cancer[18].

DEFINITION OF EARLY NADC

There is no established definition of early NADC with respect to the depth of invasion and risk of lymph node metastasis. However, previous studies have followed the rules used for early colorectal[14] or gastric cancer[19], *i.e.*, tumor invasion to the lamina propria or muscularis mucosa (T1a) or the submucosa (T1b) regardless of lymph node metastasis[11,12,20]. Based on a Japanese analysis of early NADCs that included pT1a or pT1b cancer, Nagatani *et al*[11] reported no incidence of lymph node metastasis among 40 cases of pT1a cancers, and Fujisawa *et al*[12] reported none among 166 cases of mucosal cancers. The incidence of lymph node metastasis among pT1b cancer is reported to range from 5.3% (2/37) to 5.4% (4/75)[11,12]. The depth of pT1b cancer invasion has not been described in these reported cases; therefore, at present, pT1b NADC should be considered at risk of lymph node metastasis regardless of the depth of submucosal invasion.

TREATMENT STRATEGY FOR SUPERFICIAL NADETs

Types of NADETs to be treated

It is important to determine the type of sporadic superficial NADETs that should be removed to lower the risk of those that have a substantial possibility to progress to invasive cancer and to avoid overtreatment of those with less malignant potential[21,22]. Small bowel adenomas, including duodenal adenomas, are reported to have a higher percentage of villous tumors than colorectal adenomas[5]; thus, the possibility of harboring cancer is estimated to be higher[23,24]. Patients with familial adenomatous polyposis (FAP) are known to have a high prevalence of duodenal adenomas, and prospective follow-up studies have demonstrated that such adenomas can slowly progress to cancer[24-26]. Sporadic NADC may occur because of the adenoma carcinoma sequence, as in FAP patients[15,27], or *de novo*. However, the incidence of sporadic NADC is extremely rare; thus, endoscopic findings suggestive of cancer have not yet been established.

Pretreatment evaluation of cancerous lesions

Macroscopically, larger-sized lesions, those with a component of depression (Ⅱa + Ⅱc type or Ⅱc type) and those with a red and ill-glistened surface, are reported to have a higher tendency to have a cancerous component[28,29]. In contrast, there are also a few reports of large Ⅱa type, so-called carpet-like adenomas that increase in size without cancerous components[8,28]. In addition to the macroscopic features, findings of magnifying endoscopy with[30-32] or without[33-35] narrow-band imaging can offer information to distinguish potentially malignant lesions. Heterogeneous patterns of irregular or disappeared mucosal structures with irregular vascular patterns have been correlated with high-grade dysplasia (HGD) or mucosal cancer[30,33,34].

Issue of pretreatment biopsies

The necessity of obtaining biopsy specimens from superficial NADETs before treatment remains controversial. Because of the thinness of the duodenal wall, the biopsy

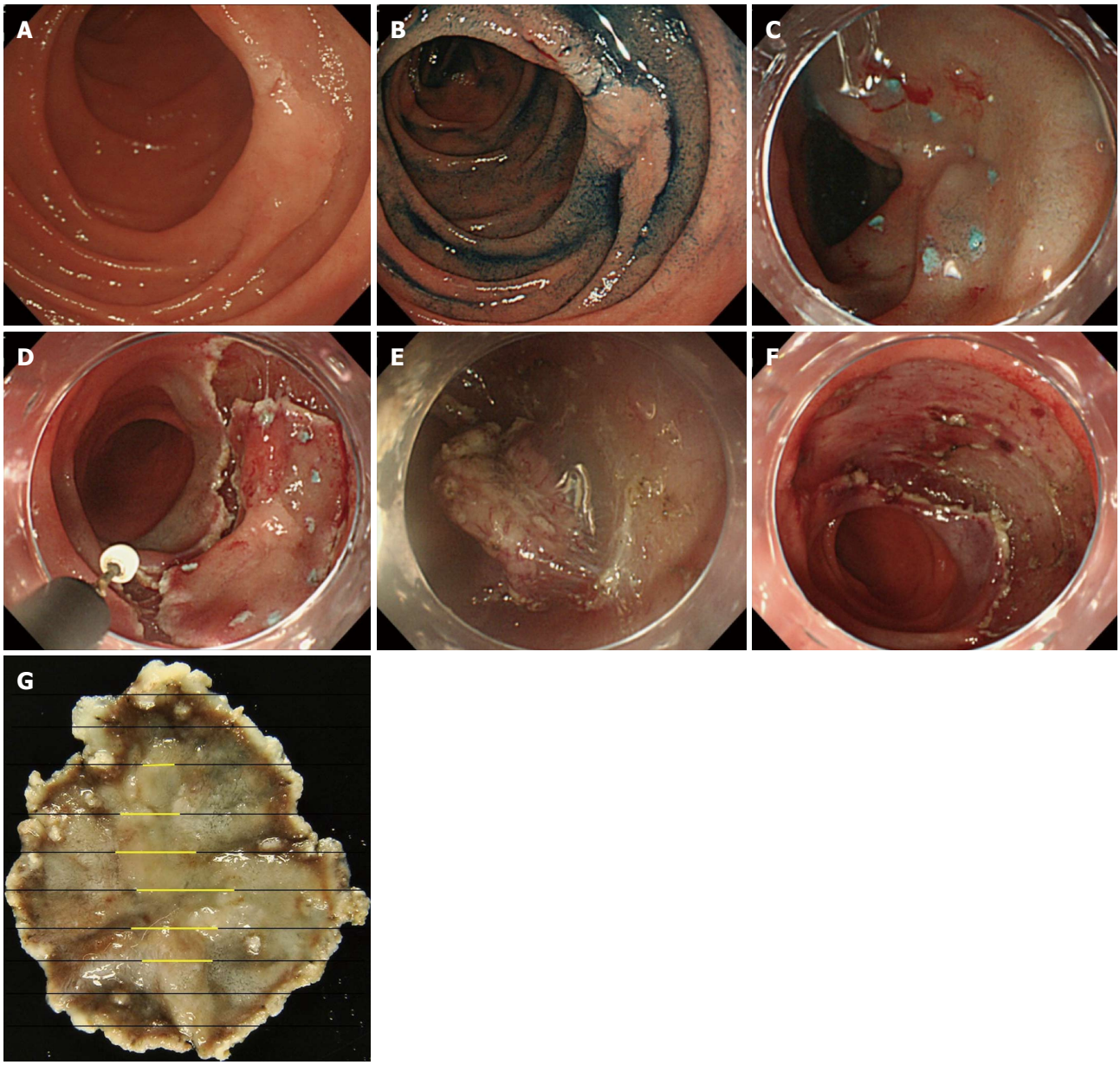

Figure 1 Images in endoscopic submucosal dissection. A: A superficial elevated type (Ⅱa) lesion is observed in the second portion of the duodenum; B: Chromoendoscopy with indigocarmine was used to clarify the border of the tumor; C: After marking with argon plasma coagulation, submucosal injection was performed; D: Circumferential cutting was performed using an insulated-tipped knife [ITknife nano (KD-612); Olympus, Tokyo, Japan]; E: Submucosal dissection was performed; F: The lesion was successfully removed en bloc without complications; G: Histopathological analysis revealed a mucosal adenocarcinoma of 16 mm in diameter (yellow lines).

procedure itself may induce unintended fibrosis associated with the lesion, which may complicate subsequent endoscopic resection (ER). In contrast, a histological proof of malignancy may be preferable before employing a treatment modality with a substantial risk of complication, such as ER or surgery. Discrepancy of endoscopic biopsy histology and that of resected specimens is sometimes experienced in gastric epithelial lesions[36] and has also been reported in duodenal lesions[20,37-39]. Post-treatment diagnosis may lead to an upgrade in pathology. In a previous study, comparisons between biopsy and resected specimens of 56 superficial NADETs revealed the same diagnosis in 59% patients, an upgrade in 36% patients, and a downgrade in 5% patients. Among the lesions with an upgrade in pathology, most had an upgrade from HGD to adenocarcinoma[40]. In another study, T1a cancer was observed in 13.5% cases in which initial biopsies indicated simple adenomas[38]. Therefore, lesions with a biopsy diagnosis of HGD should be considered for local treatment, and ER may present an improved diagnostic tool for borderline lesions.

Pretreatment evaluation between T1a and T1b NADC

It is difficult to differentiate T1a from T1b NADC by barium studies or endoscopy[11]. Nagatani *et al*[11] studied the macroscopic features of early NADC with little pos-

sibility of submucosal invasion and indicated the following lesions suggestive of T1a cancer: Ip type, ≤ 20 mm; Is type, ≤ 5 mm; IIa type, ≤ 10 mm; and carpet-like IIa type of any size. Endoscopic ultrasonography has been reported to be a promising tool for diagnosing and staging duodenal villous tumors[41,42]. Non-lifting sign or lack of mobility when manipulated with a snare suggest submucosal invasion[43].

Endoscopic treatment and outcomes

Endoscopic treatment should be limited to lesions confined to the mucosa; however, endoscopic techniques to remove superficial NADETs have not yet been standardized[44,45]. Although case reports of polypectomy[46,47] and strip biopsy[48-50] for protruded lesions have been reported, the results of endoscopic mucosal resection (EMR) for NADETs are based on several small case series[51,52]. EMR often requires multiple sessions (piecemeal resection), and complete remission has been reported in 55%-100% cases[37,38,43,53-55]. The local recurrence rate among these previous studies was 0%-37%, and recurrent lesions were endoscopically re-treated by a second EMR or endoscopic ablation[37,38,43,53-55]. Reportedly, successful eradication by endoscopic treatment is dictated by the extent of the luminal circumference of the tumor[56] and the possibility of en bloc resection[57]. Complications after EMR include bleeding (0%-33%) and perforation (3%)[38,58].

Compared with EMR, there are fewer reports of endoscopic submucosal dissection (ESD) (Figure 1) for superficial NADETs[59]. Nevertheless, ESD has been reported to have a superior complete resection rate (86%-100%), with no incidence of recurrence[20,39,40,60-63]. However, the complication rate of bleeding is 0%-7% and the perforation rate is higher at 6%-50%[20,39,40,60-63]. A retrospective multicenter survey of 421 duodenal EMR and ESD cases showed that both intraoperative and delayed perforation occurred more frequently among ESD cases[64]. In addition, there was no difference in the overall perforation rate between lesions located in the first or second portion of the duodenum; however, delayed perforation was mostly observed in the second portion[64] or distal to Vater's ampulla[65]. Delayed perforation may occur even after successful ESD[61], and the high rate of delayed perforation may be because of the larger ulcer created by ESD, increased thermocoagulation effect induced by ESD, and presence of bile and pancreatic juices. To avoid the risk of delayed perforation, attempts have been made to completely close the mucosal defect after ESD with multiple endoclips[64,66] or with an over-the-scope clip[67], or by applying polyglycolic acid sheets[68,69]. Others have reported insertion of endoscopic nasobiliary drainage and nasopancreatic drainage tubes to avoid exposure of bile and pancreatic juices to the ESD ulcer[61].

Lienert *et al*[70] reported the use of argon plasma coagulation (APC) for the treatment of duodenal adenoma in a cohort of 15 patients. Eradication was successful in 87%, no patients developed cancer during the study period of 40 mo, and the local recurrence rate was 39%[70]. However, APC treatment is inadequate to obtain a histological assessment of the entire lesion; therefore, it is risky to solely rely on APC for the treatment of superficial NADETs. Nonetheless, APC may be used as an adjunct to EMR to reduce local recurrence[71] or for locally recurrent lesions after EMR.

Surgical treatment and outcomes

An optimal surgical treatment of sporadic superficial NADETs has not yet been established. Pancreaticoduodenectomy (PD), also known as the Whipple procedure, is a radical surgery performed for advanced disease and cases of early stage NADC with the aim to avoid tumor recurrence[72-75]. Pancreatic fistula, anastomotic leakage, and pancreatitis are serious complications after PD. Although the morbidity and mortality rates following PD have decreased in recent years[76,77], the procedure still results in considerable intraoperative stress.

Transduodenal local excision[78,79], wedge resection (segmental, partial, and full-thickness)[78,80-83], and pancreas-sparing duodenectomy (PSD)[78,84,85] are organ-preserving surgical procedures suitable for patients with premalignant or early malignant duodenal lesions. In a previous study, the recurrence rate of villous duodenal tumors after transduodenal local excision was reported to be 32% at 5 years, and 24% recurrences were cancer[78]. However, the presence of cancer was not known before surgery, and the authors concluded that PD is appropriate for villous tumors with a malignant component[78]. Jurisić *et al*[82] reported local recurrence with nodal metastasis after local excision for cancer with submucosal invasion, suggesting the inadequacy of local excision for T1b NADC.

Wedge resection (segmental, partial, and full-thickness) has been associated with lower morbidity than PD[78,80,81,83,86,87]. Tanigawa *et al*[81] reported a good clinical course without recurrence after partial resection for T1a cancer. For early NADC located in the third and fourth portions of the duodenum, segmental resection is associated with negligible morbidity and mortality, while allowing for satisfactory clear margins during lymphadenectomy[83].

PSD was introduced as an alternative to PD for treatment of benign and premalignant duodenal disease and is reportedly a beneficial modality for treatment of patients with multiple lesions[78,84,85,88]. For PSD, patients should have a preoperative diagnosis of no lymphadenopathy and sampling of the lymph node surrounding the tumor before resection should be obtained for intraoperative pathological examination to detect lymph node metastasis[85]. Eisenberger *et al*[84] recommended analysis of intraoperative fresh frozen sections to exclude malignant disease and to consider conversion of the procedure from PSD to PD after intraoperative diagnosis of malignant disease in the fresh frozen sections. The incidence of local recurrence is low, suggesting that PSD is an acceptable procedure for treatment of selected duodenal neoplasms, such as superficial NADETs confined to the mucosa.

PROGNOSIS OF SUPERICIAL NADETs

Because previous reports of surgical treatment for duodenal cancer included small numbers of patients with superficial NADETs, including adenoma or early NADC, little information is available regarding treatment success and treatment-related morbidity or mortality.

The most important prognostic factor is the depth of tumor invasion[80,89-93]. With regard to the risk of nodal metastasis, superficial NADETs, including adenoma and T1a cancer, are treatable by local resection; however, the ability to achieve a negative margin may be a prerequisite to successful local resection. For adenoma or T1a cancer, ER presents the same distant survival rates as surgery[94]. In contrast, T1b cancer should be resected with lymphadenectomy and PD appears to remain the treatment of choice. In a recent review of 67 patients, Barnes *et al*[95] reported a 5-year survival rate of 100% in stage I duodenal cancer. Therefore, preoperative diagnosis of the presence of submucosal invasion is important to select the appropriate surgical method.

FOLLOW-UP AFTER TREATMENT

Considering that EMR is often performed piecemeal, repetitive endoscopy after resection is necessary. Ahmad *et al*[37] suggested that 6 wk was a suitable interval to observe healing of the EMR site for lesions requiring multiple sessions to achieve and/or confirm complete remission. Others report that endoscopic surveillance every 3 mo is required initially. Subsequently, if no recurrence is observed, the surveillance should be reduced to every 6 mo or once a year[54,96]. Annual checkups should be performed for at least 2 years after complete removal[55]. For lesions with submucosal invasion, computed tomography and abdominal ultrasound should be performed to detect nodal or distant metastasis.

Recent studies of Western populations have suggested that patients with sporadic duodenal adenomas are at a higher risk for the development of colorectal neoplasia[97-100]. The odds ratio of colorectal neoplasia among patients with sporadic duodenal adenomas is reportedly 2.4-3.6, and the incidence of colorectal cancer was significantly higher[97,98]. Dietary risk factors correlated with cancer of the small intestine are similar to those correlated with colon cancer[101]. Therefore, patients with sporadic duodenal adenomas should undergo routine colonoscopy screening to increase the detection rate of colorectal neoplasia.

FUTURE PERSPECTIVES

As with other malignancies, early detection is important for the treatment of sporadic superficial NADETs. Establishing an endoscopic diagnostic tool to differentiate the lesion between adenoma and cancer as well as between mucosal and submucosal cancer is required. For lesions confined to the mucosa, local resection is acceptable, and en bloc resection with negative margins is beneficial to lower the risk of local recurrence. The use of endoscopic treatment modalities, including EMR and ESD, for the treatment for superficial NADETs is increasing. However, ESD remains a challenging method, considering the high risk of intraoperative or delayed perforation. Therefore, primary closure of the endoscopically resected site, as a preventive measure, is preferable. The use of radical surgery for superficial NADETs has decreased with the introduction of minimally invasive surgery. Newer methods, such as the use of an over-the-scope clip[67-69] or combined surgery of endoscopy and laparoscopy[86,102], have been reported. Further studies are warranted to improve the current diagnostic and treatment methods to both preserve curability and improve the quality of life.

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