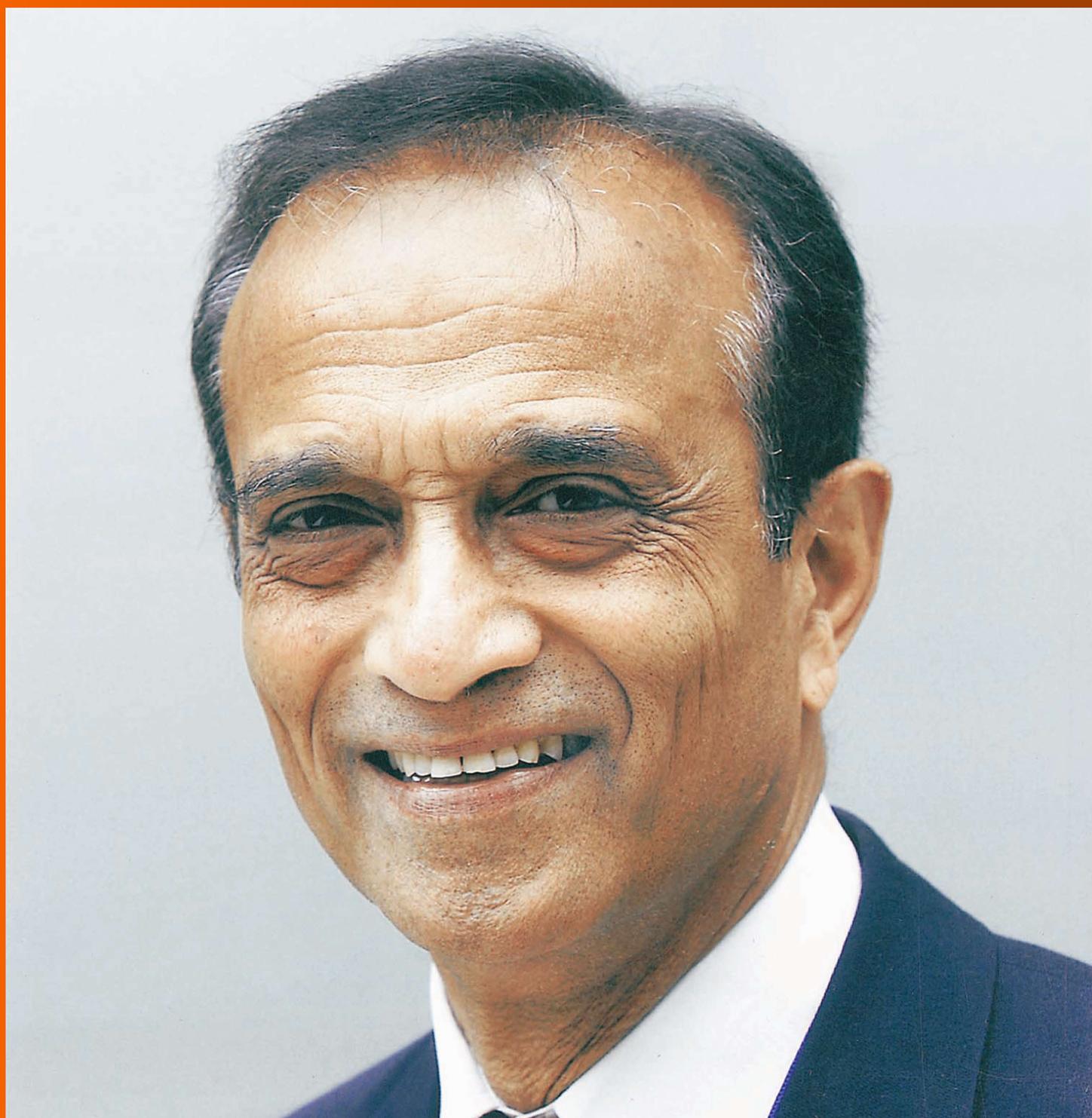


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Upfront surgery of small intestinal neuroendocrine tumors. Time to reconsider?

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Abstract

Small intestinal neuroendocrine tumors (SI-NETs) may demonstrate a widely variable clinical behavior but usually it is indolent. In cases with localized disease, locoregional resective surgery (LRS) is generally indicated with a curative intent. LRS of SI-NETs is also the recommended treatment when symptoms are present, regardless of the disease stage. Concerning asymptomatic patients with distant metastases, prophylactic LRS has been traditionally suggested to avoid possible future complications. Even the current European Neuroendocrine Tumor Society guidelines emphasize a possible effect of LRS in Stage IV SI-NETs with unresectable liver metastases. On the contrary, the 2017 National Comprehensive Cancer Network Guidelines on carcinoid tumors do not support the resection of a small, asymptomatic, relatively stable primary tumor in the presence of unresectable metastatic disease. Furthermore, a recent study revealed no survival advantage for asymptomatic patients with distant-stage disease who underwent upfront LRS. At the aforementioned paper, it was suggested that delayed surgery as needed was comparable with the upfront surgical approach in terms of postoperative morbidity and mortality, the length of the hospital stay and the rate of incisional hernia repairs but was associated with fewer reoperations for bowel obstruction. On the other hand, it is also important to note that some patients might benefit from a prophylactic surgical approach and our attention should focus on identifying this patient population.

Key words: Small intestinal neuroendocrine tumors; Locoregional resective surgery

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Core tip: Upfront locoregional resective surgery of small intestinal neuroendocrine tumors is the mainstay treatment when radical resection is feasible or when symptoms are present, regardless of the disease stage. However, in the light of contemporary evidence, the traditional upfront surgical approach is challenged regarding patients with distant metastases without local tumor-related symptoms.

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INTRODUCTION

Small intestinal neuroendocrine tumors (SI-NETs) have an indolent clinical course and are often diagnosed at a late stage^[1]. In patients without distant metastases, locoregional resective surgery (LRS) is generally indicated with a curative intent. However, in patients with distant-stage disease, LRS is generally not considered curative, although sometimes liver surgery or local ablative treatments are undertaken after or before radical LRS.

Even in the era of a broad panel of novel, targeted and systemic therapies for SI-NETs, recurrence after perceived radical liver resection is still very common, and neither liver resection nor radiofrequency ablation of liver metastases has unequivocally been found to prolong survival^[2,3]. Therefore, even with the intention to achieve macroscopic radicality and cure, liver procedures for SI-NETs should generally be considered palliative^[4].

STUDY ANALYSIS

Many patients with distant-stage disease may present with distinct clinical symptoms and signs due to hormonal excess and/or with local tumor-related symptoms causing abdominal pain, obstruction and/or an impaired blood supply to the intestines. These patients with local tumor-related symptoms generally undergo LRS at the time of diagnosis. Some patients may undergo an acute laparotomy because of an intestinal obstruction of unknown etiology. Others will undergo palliative surgery for a partial intestinal obstruction, bleeding, ischemic complications due to a tumor mass, or even for symptom relief in the cases of hormonal syndrome refractory to medical therapy.

The extension of mesenteric lymph node metastases below or above the horizontal part of the duodenum is a crucial factor for treatment since a number of patients will display mesenteric lymph node metastases in the root of the mesentery, with associated fibrosis, encasing

the superior mesenteric vessels. These tumors are then usually considered inoperable. Palliative, minimally invasive measures such as stenting of the superior mesenteric vein have been applied to symptomatic patients with bulky mesenteric disease since LRS in these patients may be complicated and endanger circulation to substantial parts of the bowel^[5].

Generally, for tumors originating in the proximal ileum and jejunum, segmental small intestinal resection is performed. However, for primary tumors located near the ileocecal valve in the distal ileum, ileocecal resection or right hemicolectomy is performed, with the latter possibly combined with improved clearance of regional lymph node metastases. Even though the latest Surveillance Epidemiology and End Results report challenges the prognostic significance of lymphatic metastasis for SI-NETs with locoregional disease only, there are certain biases and limitations in these data^[6].

In asymptomatic patients with distant metastases, prophylactic LRS has been traditionally advocated to avoid a future intestinal obstruction, ischemia, perforation or bleeding. The survival rates of these patients after LRS, as reported in retrospective cohort studies, are probably largely influenced by both the selection bias and immortal time bias. Generally, there are differences in contemporary literature from up-to-date guidelines about approaching endocrine disorders^[7]. The current ENETS guidelines emphasize a possible effect of LRS in Stage IV SI-NETs with unresectable liver metastases, but these guidelines are based on the information gathered from the abovementioned cohort studies^[8,9].

On the other hand, the 2017 National Comprehensive Cancer Network Guidelines on carcinoid tumors advocate against resection of a small, asymptomatic, relatively stable primary tumor in the presence of unresectable metastatic disease^[10]. A recent study has revealed no survival advantage for asymptomatic patients with distant-stage disease who underwent upfront LRS^[11]. Interestingly, delayed surgery as needed was comparable with the upfront surgical approach in terms of postoperative morbidity and mortality, the length of the hospital stay and the rate of incisional hernia repairs but was associated with fewer reoperations for bowel obstruction^[12]. These results are also consistent with the Rotterdam group findings that confirmed that there is no benefit of prophylactic surgery for overall survival^[12]. However, it is also important to note that while patients with disseminated SI-NETs may not benefit from upfront prophylactic surgery, some patient populations might, *e.g.*, older patients or those with large tumors and patients with progressive locoregional disease^[13]. Importantly, to be able to identify patients who might benefit from a prophylactic surgical approach, more insight is needed into the development of mesenteric fibrosis in SI-NETs^[9].

PERSPECTIVE

In conclusion, LRS retains its value in the treatment of patients with SI-NETs when radical resection is feasible

or symptomatic disease is present, regardless of the disease stage.

However, current evidence challenges the traditional view that extensive LRS needs to be performed in patients with distant metastases in the absence of local tumor-related symptoms. A more conservative approach, with delayed LRS as clinically indicated, may be reasonable for the subset of asymptomatic SI-NET patients with distant-stage disease. This revised approach may complete the armamentarium of systemic and liver-directed treatments as indicated per patient.

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