Viewpoint

Management of neuroendocrine liver metastasis: Searching for new prognostic factor and appraising repeat hepatectomy

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Gastro-enteric and pancreatic neuroendocrine neoplasm (NEN) is categorized as a borderline malignant tumor and was historically called carcinoid, meaning carcinoma-mimicking. NEN tumors usually grow slower than most carcinoma tumors originating from visceral organs; however, some metastasize to lymph nodes or the liver, and are potentially life-threatening. One of the unique characteristics of NEN among various malignant or borderline malignant neoplasms is that tumor grade determined by histological examination has the strongest impact on patient prognosis. Differentiated NENs are classified as grade 1 to 3 on the basis of Ki-67 value, and this grade correlates well with the development of lymph node and liver metastases, and even the overall survival (OS) of patients. However, this tumor grading is impossible unless a sufficient amount of tumor specimen is obtained by needle biopsy or tumor resection. Therefore, it would be useful if imaging features of NEN tumors could be used to predict tumor behavior, particularly when an indication of surgical resection is considered.

Armstrong *et al.* recently addressed the prognostic impact of enhancing patterns in dynamic computed tomography (CT) scans and calcification findings in plain CT scans in patients undergoing surgery for neuroendocrine liver metastasis (NELM) (1). In a previous study, enhancing patterns in primary NEN tumors identified on dynamic CT were analyzed, showing that a hypo-enhancing finding in the arterial phase was associated with higher tumor grade, lymph node metastasis, synchronous liver metastasis, and poorer OS (2). Another study demonstrated that a calcification finding in unenhanced CT of pancreatic NEN tumor was associated with higher tumor grade, larger tumor size, lymph node metastasis, and synchronous liver metastasis, although it did not impact on OS (3). Contrary to the results of these two previous studies, Armstrong *et al.* could not demonstrate any relationship with clinicopathological factors of either hypo-enhancing or calcification findings of NELM (1). They estimated that tumor biological behavior was worse or had already turned worse in patients with NELM, which may explain the above-mentioned discrepancies in the results. Because of the limited number of cases and the retrospective nature of their study, the results were not conclusive; however, their study is important in that prognostic factors obtained preoperatively were assessed in the field of NELM, for which the literature is scarce.

To analyze the long-term survival of patients undergoing surgical resection for NELM, the treatment choice for recurrent tumors after initial hepatic resection is important. However, no information regarding treatments for recurrent tumors was described in the study by Armstrong *et al.* Treatment choice after NELM recurrence was reported to be correlated with long-term survival of patients (4). Therefore, such information would help the understanding of the above-mentioned discrepancies; in particular, the number of patients undergoing surgical resection of recurrent tumors in each imaging category would be useful. If enhancing patterns or calcified findings of NELM tumors in CT are correlated with tumor biology, the situations of NELM tumors at recurrence,

namely, tumor number, tumor size, or distribution in the liver, which may impact on the resectability of recurrent tumors, would differ according to such imaging findings. From another point of view, differences in the proportion of patients undergoing resection of recurrent tumors may affect the long-term results. Some patients in whom resection is possible but abandoned on the basis of pessimistic idea for tumor recurrence may lose the chance of long-term survival.

The majority of patients undergoing initial NELM resection experience tumor recurrence, most of which is observed in the liver. However, a consensus of the treatment strategy for recurrent tumors has not yet been achieved, mainly because of the paucity of the literature. Recently, we reported the efficiency of repeat hepatectomy of recurrent NELM tumors through an investigation of the long-term results of patients with recurrence (5). This study reported a higher 5-year OS rate (79%) after repeat hepatectomy than that without (35%). Furthermore, the recurrence-free survival (RFS) curve after initial hepatectomy was similar to that after repeat hepatectomy, which also indicated the usefulness of repeat hepatectomy. Another study by Spolverato *et al.* demonstrated the utility of repeat hepatectomy for recurrent NELMs through a multi-institutional retrospective study (6). In this study, repeat hepatectomy of recurrent tumors resulted in a 10-year OS rate of 60%.

Another concern in the field of NELM treatment is whether a 'cure' can be achieved using an aggressive strategy. Although OS after resection of NELM is not desperate because of the slow-growing nature of NEN tumor, most patients develop recurrence after initial hepatectomy of NELM. Through strict postoperative follow-up of the patients at our own outpatient clinic, 10-year RFS after initial hepatectomy was less than 10% (5). In the field of surgery for colorectal liver metastasis, RFS after initial hepatectomy is also low; however, a cure can be expected after one or more repeat hepatectomies even after tumor recurrence (7). In this context, we recently calculated the recurrence-free interval after the 'last' hepatectomy, in other words, the 'most recent' hepatectomy for NELM in each patient. Among 49 patients undergoing initial hepatectomy for NELM, the longest 'last' recurrence-free interval was 14.8 years, followed by 9.8 years, and 7.3 years (data not published). Disease cure after NELM resection is possible, though not expected in many patients. Moreover, a strategy using aggressive repeat hepatectomies provides favorable long-term survival [10-year OS rates of 52% (6) and 70% (5)].

To improve the prognosis of patients with NELM, the timing and indication of surgical resection of initial and recurrent NELM tumors are critical because surgical resection has the strongest prognostic impact, but a high rate of tumor recurrence is estimated. Although Armstrong *et al.* could not identify any CT findings as prognostic factors (1), it would be useful to determine the surgical indication and timing based on any factor that is available before surgery; for example, imaging findings of not only CT scans, but also magnetic resonance imaging, fluorodeoxyglucose positron emission tomography, and somatostatin receptor scintigraphy that predict the efficiency of surgery.

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Footnote

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