Table 1. Multivariate analysis of independent prognostic factors

Variable	p	Hazard ratio	95% CI
Preoperative CEA level (<5.0 vs. ≥5.0)	0.0075	1.508	1.069–2.123
Vessel invasion (negative vs. positive)	0.0140	1.466	1.026–2.096
MLN number (1 vs. ≥2)	0.0332	1.783	1.087–2.915
MLN number (≤6 vs. ≥7)	0.0004	2.169	1.332–3.534

CEA = Carcinoembryonic antigen; MLN = metastatic lymph nodes.

Table 2. Multivariate analysis of risk factors related to a recurrence

Variable	χ^2	p	Hazard ratio	95% CI
Sphincter-preserving operation (yes/no)	23.678	<0.0001	1.872	1.454–2.410
Depth of invasion (a1/a2)	21.546	<0.0001	1.817	1.412–2.338
Lymphatic invasion (negative/positive)	26.538	<0.0001	1.876	1.876–4.062
MLN (negative/positive)	78.637	<0.0001	3.403	2.596–4.461
MLN of lateral pelvis (negative/positive)	67.860	<0.0001	6.830	4.324–10.788
Actual measurement of ME (<5 mm/≥5 mm)	25.961	<0.0001	1.048	1.048–1.110

MLN = Metastatic lymph nodes; ME = mesorectal extension.

Discussion

Grasping cancer progression as a prognostic factor is extremely important when choosing adjuvant chemotherapy and in constructing effective postoperative follow-up systems. Indicators that are strongly associated with prognosis and easily defined are therefore crucial. Lymph node metastasis is an important prognostic factor for colorectal cancer [1, 5–7]. Various studies about relationships between lymph node metastases and prognosis have been reported. Tapper et al. [9] and Nelson et al. [10] mentioned that staging for colorectal cancer requires retrieval of 12–17 lymph nodes. Kim et al. [11] mentioned that retrieval of >10 lymph nodes offers almost certain identification of metastasis to lymph nodes, and tumor differentiation and T stage seem to correlate with higher nodal metastasis rate. Schumacher et al. [12] and Vaccaro et al. [13] recently reported that the lymph node ratio, representing the ratio of the number of MLNs to the number of retrieved lymph nodes, is associated with prognosis. However, whether the classification by the number of MLNs reflects prognosis has yet to be evaluated. For standardization of lymphadenectomy, the extent of lymphadenectomy has been regarded as important in JCCRC. In Japan, Matsuda et al. [14] recently reported no significant difference between N1 and N2 by conventional classification of MLNs. Furthermore, Suzuki et al. [15] also reported that classification by the number of MLNs predicted prognosis better than classification by level of MLNs in node-positive colon cancer. From a retrospective study in our institution, both classification by number of MLNs and level of MLNs revealed a difference in prognosis (data not shown). In the TNM classification the degree of MLNs has used a cutoff of 3 metastatic nodes since the first edition of the classification.

Hermanek et al. [16] reported that the prognosis of colorectal cancer with more than four parabowel MLNs was approximately the same as with MLNs along a principal trunk artery. Since the fifth edition of the TNM classification in 1997, the degree of MLNs was modified disregarding the location of MLNs. Former N3 cases were integrated into N1 and N2 subcategories according to the number of MLNs (N1 ≤3, N2 >3) [17]. Kendal [18] reported that the classification of MLNs was a prognostic factor for rectal cancer, lung cancer and gastric cancer, when the number of MLNs was categorized using a cutoff of 3 metastatic nodes (N1 ≤3, N2 >3).

On the other hand, Vaccaro et al. [6] reported that the presence of >3 positive nodes was significantly associated with poorer survival rates in uni- and multivariate analyses. As for the data in our institution, the group with only 1 MLN showed a significantly better prognosis than the group with >1 MLN. The group with ≥7 MLNs showed a very poor prognosis. These classifications represented an independent prognostic factor in multivariate analysis. It is thought that when several symptom example numbers and progression to rectal cancer were included in the background, metastasis to >7 MLNs resulted in a very poor outcome. As more detailed examinations demonstrated approximately similar results, the number of MLNs was suggested to sufficiently reflect a contribution to prognosis. However, the precision of a diagnosis of metastasis to lymph nodes is concerned with personal factors such as range of dissection, dissection maneuvers, and treatment of the specimens. In addition, the number of lymph nodes in the location of the tumor is dependent on the host. Shen et al. [19] also reported the number of lymph nodes obtained in specimens of colorectal cancer as being significantly associated with the length of resected bowel, patient age, and tumor location. There is clearly more room for further examination of MLN degree.

In reports from Europe and America, the cut-off value set by measuring ME for rectal cancer reportedly correlates with recurrence and prognosis [20]. Few reports have concretely described methods of measuring ME [20–22]. Vague phrases such as 'perirectal fat invasion' [23] or 'mesorectal invasion' [24, 25] have been used in other reports. Cawthorn et al. [20] reported that in order to set cut-off values of ME to 4 mm, 5-year survival rate must be higher for the group with ≤4 mm in both stage II and stage III. Merkel et al. [26] classified pT3 into pT3a (≥5 mm invasion) and pT3b (<5 mm invasion), and analyzed data from the Erlangen Registry for Colorectal Carcinoma and the Study Group for Colorectal Carcinoma. Wittekind et al. [27] reported that the group with ME <5 mm showed higher survival rates in data from the Swiss Registration Study Colorectal Cancer. Miyoshi et al. [21] from Japan reported that ME >6 mm is independently associated with poor prognosis in pT3 lower rectal cancer.

Some reports have described the value of ME being associated with local recurrence, although ME was defined in a slightly different manner [24, 26]. Setting cut-off values for ME may also be achieved by considering overall survival rate [20, 23, 26], relapse-free survival rate or recurrent rate [24, 25]. In terms of pT3 in the TNM classification, subdividing degree of ME into four T categories (pT3a to pT3d) has been suggested to reveal incremental differences [27]. It is clinically important how the degree of ME reflects for staging and whether ME can become a prognostic factor beyond the current staging system.

From some reports, including our own data, measurement of ME may reflect clinically prognostic predictors and judgment of need for adjuvant therapy. Again, this area warrants further investigation. With these results and reports, some problems seem to remain in staging systems for colorectal cancer. The number of MLNs clearly influences the prognosis of colorectal cancer. In addition, in rectal cancer without adventitia, measurement of histological ME is clinically important. Further examinations will help to clarify how these factors can be applied to daily medical treatment.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of the article.

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