Original article

Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery

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Background: The aim of this study was to assess the impact of inferior mesenteric artery (IMA) root nodal dissection before high ligation of the artery on survival in patients with sigmoid colon or rectal cancer.

Methods: Data on 1188 consecutive patients who underwent resection for sigmoid colon or rectal cancer, with high ligation of the IMA, were identified from a prospective database (April 1965 to December 1999). Survival of patients with involvement of nodes along the IMA proximal to the origin of the left colic artery (root nodes, station 253) through the bifurcation of the superior rectal artery (trunk nodes, station 252) was determined.

Results: Twenty patients (1·7 per cent) had metastatic involvement of station 253 lymph nodes and 99 (8·3 per cent) had metastases to station 252. The 5- and 10-year survival rates of patients with metastases to station 253 were 40 and 21 per cent, and those for patients with metastases to station 252 were 50 and 35 per cent, respectively.

Conclusion: High ligation of the IMA allows curative resection and long-term survival in patients with cancer of the sigmoid colon or rectum and nodal metastases at the origin of the IMA.

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Introduction

During surgery for sigmoid colon or rectal cancer, the inferior mesenteric artery (IMA) may be ligated at a point just below the origin of the left colic artery (low ligation) or at the origin of the IMA directly from the aorta (high ligation). The high-ligation technique enables *en bloc* removal of additional lymphatic drainage from cancers at and around the origin of the IMA, but it is unclear whether this confers a survival advantage.

There have been no prospective controlled or randomized studies of high *versus* low ligation. Guidelines published by Nelson *et al.*[1] recommend low ligation for rectal cancer surgery, except when metastases to lymph nodes beyond the origin of the left colic artery are suspected. However, this recommendation is based on the data from one French randomized trial in patients with left colonic cancer[2].

No study has investigated the detailed anatomical distribution of lymph node metastases along the IMA in a large series in which high ligation was performed routinely. The few studies on this issue included limited numbers of patients with colorectal cancer, ranging from 129 to 198[3–5]. Other studies have reported details of such lymph node distributions, but only in patients who underwent colorectal cancer resection and whose operative findings indicated the need for high ligation of the IMA[4,6,7]. This type of intraoperative determination is known to be unreliable[8]. At present, the true distribution of lymph node metastasis along the IMA in patients with sigmoid colon or rectal cancer who undergo potentially curative resection is unknown.

Some favourable outcomes after high ligation may be attributable to the stage migration phenomenon, which may arise as a result of more accurate staging owing to more extensive lymphadenectomy[6,9,10]. A proportion of patients will therefore be assigned to a more advanced stage than would otherwise be the case, although their prognosis is the same. If this occurs, the overall results in

each stage improve and the proportion of patients in more advanced stages increases[11].

The present study was a prospective analysis of the largest known series of curative resections for sigmoid colon or rectal cancer in which high ligation was performed routinely. The study was designed to circumvent the stage migration effect in order to provide direct information on the significance of lymph node metastases along the IMA. The aim was to evaluate whether patients with sigmoid colon or rectal cancer and metastasis in certain nodes that are left behind after low ligation would benefit from high ligation in terms of curability of resection and survival.

Patients and methods

Since the foundation of the Aichi Cancer Centre Hospital, high ligation of the IMA for proximally extended lymph node dissection in patients with sigmoid colon or rectal cancer has been adopted as a standard procedure, except when adequate exposure to allow ligation of the IMA on the aorta is considered too hazardous. Data on 1361 consecutive patients who had histologically proven adenocarcinoma of the sigmoid colon or rectum and who underwent high ligation of the IMA between April 1965 and December 1999 were documented prospectively. Dissection of all lymph nodes surrounding the root of the IMA was performed before IMA ligation and excision flush with the aorta, irrespective of the operative findings with regard to the presence or absence of lymph node metastasis (*Fig. 1*).

Eighteen patients with cancers confined to the mucosa were excluded. To examine the curative value of apparently complete resection of lymph nodes along the IMA, 155 patients in whom there was clear evidence of surgical incurability were also excluded. These patients had either macroscopic or microscopic residual tumour tissue left at operation, or underwent macroscopically complete resection of hepatic or peritoneal metastases. A total of 1188 patients remained eligible, and these formed the study population.

Rectal tumours were sited as follows: lower rectum (below the peritoneal reflection), upper rectum (above the peritoneal reflection) and rectosigmoid. Lateral pelvic lymphadenectomy was used for lower rectal cancer with T2 or deeper invasion. Twenty-nine of the patients with Dukes' C lower rectal cancer received adjuvant radiotherapy. Adjuvant chemotherapy, mainly using oral 5-fluorouracil prodrugs (uracil and tegafur, UFT), was administered to patients with Dukes' A (15 sigmoid colon, 56 rectal), Dukes' B (57 sigmoid colon, 88 rectal) or Dukes' C (57 sigmoid colon, 179 rectal) tumours deemed to be at high risk for metastasis.

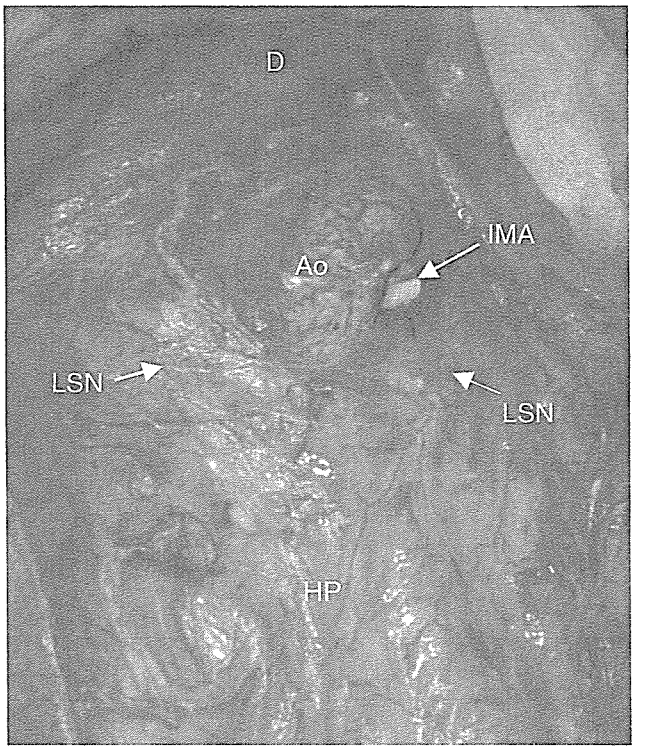


Fig. 1 High ligation of the inferior mesenteric artery at its origin from the aorta. Ao, aorta; D, duodenum, HP, hypogastric plexus; IMA, inferior mesenteric artery; LSN, lumbar splanchnic nerve

Level of ligation of inferior mesenteric artery and pathological examination of lymph nodes

The inferior mesenteric lymph nodes conglomerate around the origin of the IMA, and their location has been defined ambiguously as both the root and the periphery[12]. The Japanese criteria (Japanese Society for Cancer of the Colon and Rectum, JSCCR)[13] define the nodes at the origin of the IMA (station 253) as those nodes that lie along the IMA proximal to the origin of the left colic artery (*Fig. 2*). They define the inferior mesenteric trunk nodes (station 252) as those nodes that lie along the IMA from distal to the origin of the left colic artery to the bifurcation of the superior rectal artery. A high ligation was defined as ligation of the IMA at its root and including dissection of station 253 nodes. A low ligation was defined as ligation of the IMA at or below the level of the origin of the left colic artery and removal of the pericolic and intermediate groups of lymph nodes only, including station 252 nodes, with the primary cancer.

All regional lymph nodes were dissected individually from the adipose connective tissue of the specimen immediately after resection by the surgeons who performed the operation. Node numbers and locations were recorded on

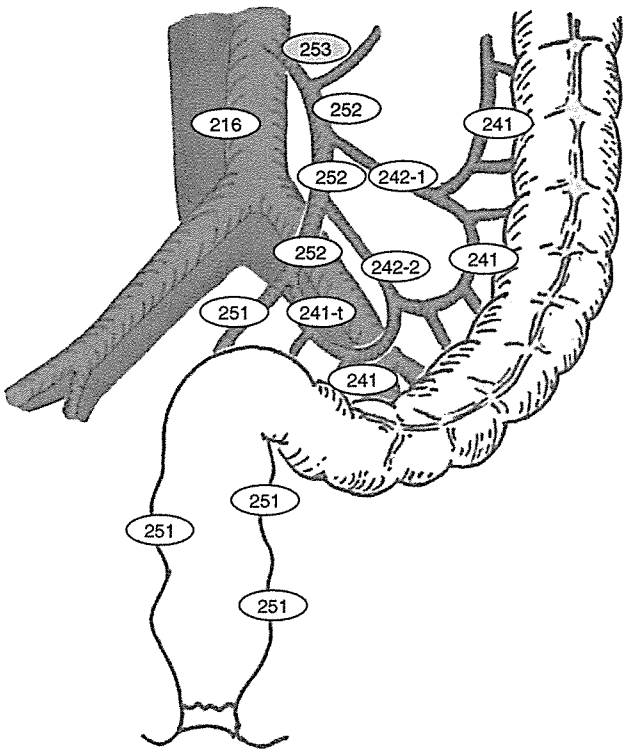


Fig. 2 Japanese Society for Cancer of the Colon and Rectum classification of lymph nodes[13] (shaded ovals denote inferior mesenteric lymph nodes)

a lymph node map (*Fig. 2*). Nodes were assigned to the appropriate station according to the classification of the JSCCR. Nodes found at each station were labelled and sent for pathological assessment. This system, which is standard practice in Japan, yields an exact topographical representation of the nodes combined with their number. Fat clearing methods were not used to collect lymph nodes from the specimen. All specimens were formalin fixed and paraffin embedded. A single section for each lymph node was routinely examined. Sections of 4 μm were cut and stained with haematoxylin and eosin for histological analysis. Special attention was paid to evaluation of the incidence of metastasis to lymph node stations 252 to 253 in relation to the tumour site, depth of invasion and survival data.

Statistical analysis

Overall and cancer-specific survival of patients with lymph node metastases along the IMA was calculated for each nodal station by the Kaplan–Meier method, irrespective of metastasis to other lymph node stations. Operative deaths were not excluded from the survival analysis. Follow-up data were documented prospectively.

Results

The characteristics of the 1188 patients who underwent potentially curative resection with high ligation are shown in *Table 1*. The overall hospital mortality rate was 0·2 per cent (three of 1188). The overall morbidity rate was 31·5 per cent (374 of 1188). Three hundred and forty-seven patients (29·2 per cent) had one or more surgical complications.

The mean number of nodes examined per patient was 28·6. A total of 107 patients had nodal involvement at stations 252 and/or 253. The incidence of metastasis to station 252 nodes was 8·3 per cent (99 of 1188). Station 252 nodal metastases occurred more frequently in patients with pT3 and pT4 lower rectal cancer (*Table 2*). The incidence of metastasis to station 253 nodes was 1·7 per cent (20 of 1188); this represented the frequency of residual metastatic nodes that would normally have been left behind in a low ligation. Of the 20 patients with station 253 nodal metastases, eight did not have cancer deposits in the station 252 nodes studied, that is they demonstrated skip metastases. There was a steady increase in the rate of

Table 1 Characteristic of 1188 patients who underwent a high ligation with curative intent

	No. of patients
Age (years)*	58·6 (59) (23–86)
Sex ratio (F:M)	482:706
Site of primary tumour	
Sigmoid colon	421 (35·4)
Rectosigmoid	202 (17·0)
Upper rectum	216 (18·2)
Lower rectum	349 (29·4)
Type of resection	
Sigmoidectomy	393 (33·1)
High anterior resection	141 (11·9)
Low anterior resection	329 (27·7)
Abdominoperineal resection	286 (24·1)
Hartmann's operation	15 (1·3)
Total pelvic exenteration	10 (0·8)
Other	14 (1·2)
Other surgery	
Lateral pelvic node dissection	301 (25·3)
Postoperative death	3 (0·2)
Postoperative morbidity	374 (31·5)
Urinary or sexual dysfunction	103 (8·7)
Ileus	77 (6·5)
Urinary tract infection	47 (3·9)
Wound infection	42 (3·5)
Anastomotic leakage	39 (3·3)
Intraabdominal or pelvic infection	39 (3·3)
Non-surgical (cardiac, respiratory, renal, cerebral)	27 (2·3)
No. of lymph nodes examined per patient*	28·6 (22·6) (7–115)

Values in parentheses are percentages unless otherwise indicated; *values are mean (median) (range).

Table 2 Nodal metastases to station 252

	Incidence of metastasis				
	pT1	pT2	pT3	pT4	Total
Sigmoid colon	2 of 100 (2)	0 of 67 (0)	7 of 169 (4·1)	5 of 85 (6)	14 of 421 (3·3)
Rectosigmoid	0 of 21 (0)	4 of 37 (11)	12 of 110 (10·9)	5 of 34 (15)	21 of 202 (10·4)
Upper rectum	1 of 30 (3)	0 of 51 (0)	13 of 105 (12·4)	3 of 30 (10)	17 of 216 (7·9)
Lower rectum	1 of 42 (2)	6 of 119 (5)	36 of 164 (22·0)	4 of 24 (17)	47 of 349 (13·5)
Total	4 of 193 (2·1)	10 of 274 (3·6)	68 of 548 (12·4)	17 of 173 (9·8)	99 of 1188 (8·3)

Values in parentheses are percentages. pT, pathological tumour stage.

positivity in station 253 nodes with increasing depth of invasion, irrespective of the tumour location; however, no station 253 nodal metastases occurred in patients with pT1 cancer (*Table 3*). Mean positive node yields of 2·0 from station 252 and 1·9 from station 253 were obtained from patients with nodal involvement along the IMA (*Table 4*).

Follow-up continued until January 2005 for all eligible patients. The median follow-up period for survivors was 79·3 months. Follow-up was completed in all patients with nodal metastases along the IMA. Actuarial overall survival rates were 50 (95 per cent confidence interval (c.i.) 41 to 60) per cent at 5 years and 35 (95 per cent c.i. 24 to 46) per cent at 10 years in patients with metastases to station 252, and 40 (95 per cent c.i. 19 to 62) per cent at 5 years and 21 (95 per cent c.i. 2 to 41) per cent at 10 years in patients with metastases to station 253 (*Fig. 3*). The cancer-specific survival rates were 53 (95 per cent c.i. 43 to 64) per cent at 5 years and 41 (95 per cent c.i. 30 to 53) per cent at 10 years in patients with metastases to station 252, and 42 (95 per cent c.i. 20 to 64) per cent at 5 years and 23 (95 per cent c.i. 2 to 43) per cent at 10 years in patients with metastases to station 253 (*Fig. 4*).

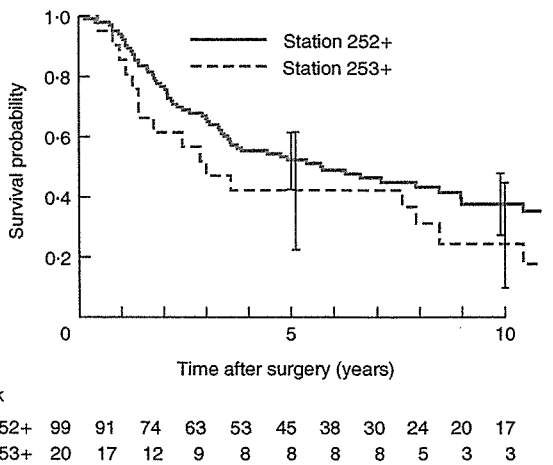


Fig. 3 Overall survival curves for patients with sigmoid colon or rectal cancer who underwent high ligation, according to inferior mesenteric lymph node status. +, Metastatic nodal disease present. Vertical bars represent 95 per cent confidence intervals

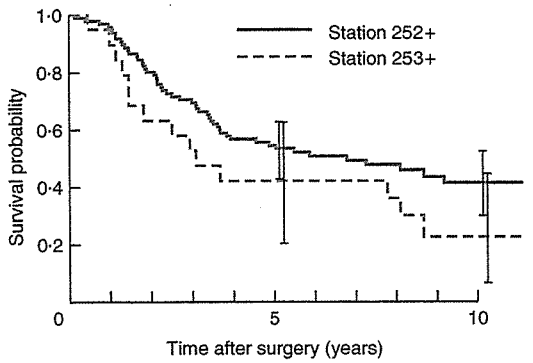
Discussion

In 1908, Moynihan[14] advised high ligation of the IMA in resections for cancer of the sigmoid colon or upper rectum. However, because the oncological effectiveness of high ligation of the IMA is not generally accepted, the level at which the IMA is ligated in operations for sigmoid colon or rectal cancer has varied greatly[3,4,7,15–20], depending largely on the surgeon[6,20]. Recent reports have shown a stage-specific survival benefit of high ligation[6,9,10]. However, these studies did not eliminate the stage migration phenomenon and failed to show a survival

Table 3 Nodal metastases to station 253

	Incidence of metastasis					
	pT1	pT2	pT3	pT4	Total	Skip Metastasis*
Sigmoid colon	0 of 100 (0)	1 of 67 (1)	2 of 169 (1·2)	3 of 85 (4)	6 of 421 (1·4)	4 of 421 (1·0)
Rectosigmoid	0 of 21 (0)	0 of 37 (0)	3 of 110 (2·7)	1 of 34 (3)	4 of 202 (2·0)	2 of 202 (1·0)
Upper rectum	0 of 30 (0)	0 of 51 (0)	2 of 105 (1·9)	0 of 30 (0)	2 of 216 (0·9)	0 of 216 (0)
Lower rectum	0 of 42 (0)	0 of 119 (0)	7 of 164 (4·3)	1 of 24 (4)	8 of 349 (2·3)	2 of 349 (0·6)
Total	0 of 193 (0)	1 of 274 (0·4)	14 of 548 (2·6)	5 of 173 (2·9)	20 of 1188 (1·7)	8 of 1188 (0·7)

Values in parentheses are percentages. *Node positive at station 253 without nodal involvement at station 252. pT, pathological tumour stage.



No. at risk

Station 252+	99	91	74	63	53	45	38	30	24	20	17
Station 253+	20	17	12	9	8	8	8	8	5	3	3

Fig. 4 Cancer-specific survival curves for patients with sigmoid colon or rectal cancer who underwent high ligation, according to inferior mesenteric lymph node status. +, Metastatic nodal disease present. Vertical bars represent 95 per cent confidence intervals

Table 4 Frequency of positive nodes in patients with nodal involvement along the inferior mesenteric artery

	Frequency of positive nodes	
	No. of positive nodes	No. of nodes harvested*
Station 252	2·0 (1·0) (1–16)	5·8 (5·0) (1–23)
Station 253	1·9 (1·0) (1–6)	3·2 (3·0) (1–10)

*Values are mean (median) (range).

advantage for patients with advanced node metastases. Furthermore, other recent series did not find any survival benefit after high ligation[4,7,19,20]. There has been no randomized or prospective study of high *versus* low ligation in patients with sigmoid colon or rectal cancer.

This prospective (but uncontrolled) study introduced a novel concept[21] for evaluation of the effectiveness of high ligation in sigmoid colon or rectal cancer surgery. The methodological approach was based on the assumption that patients who survived in the long term after resection of lymph node metastases would not have done so if the involved lymph nodes had been left *in situ*. The frequency of metastasis in nodal stations that would be left behind after low ligation of the IMA was evaluated, and the therapeutic effect of node dissection was determined by examining the incidence of metastases and the survival rates of patients with nodal deposits in those particular stations, irrespective of nodal metastases to any other lymph node station.

Potentially curative resection was achieved in 20 patients with involvement of nodal station 253, and 5-year overall and cancer-specific survival rates were 40 and 42 per cent respectively. These results demonstrate the therapeutic benefit of high ligation, because there would probably have been no long-term survivors if low ligation had been performed. However, the benefit of routine use of high ligation in patients undergoing curative resection was low (1·7 per cent, 20 of 1188) and only 0·7 per cent of patients with sigmoid colon or rectal cancer are likely be cured by high ligation of the IMA (incidence rate of metastasis 1·7 per cent, times survival rate 42 per cent). This low incidence of metastasis in the lymph nodes at the base of the IMA does not undermine the rationale behind high ligation of this artery. Surgery must always be performed for the greater good of the patient, especially if it can be carried out without adding appreciably to the risk. The negligible operative mortality and morbidity rates in this study confirm that high ligation of the IMA can be performed safely. Urinary or sexual dysfunction was the most frequent postoperative complication. Three hundred and one of the patients with lower rectal cancer also underwent lateral pelvic lymph node dissection. The autonomic nerves are intentionally sacrificed or preserved depending on whether the cancer has spread to them. This additional step is considered to be the major cause of such complications.

Five-year survival rates after low ligation in patients with involvement of middle-level lymph nodes (station 252) along the IMA of 20·5 per cent[6] and 32 per cent[22] have been reported. In the present study, patients with involvement of nodal station 252 had appreciably higher survival rates (more than 50 per cent) after high ligation, suggesting a positive effect of high ligation of the IMA on survival. Resection with curative intent could be achieved by high ligation in 107 patients with nodal involvement at stations 252 and/or 253. Because some of these nodes are left behind in a low ligation, high ligation increased the curative resection rate by 9·0 per cent (107 of 1188) at worst (assuming that low ligation would have involved ligation of the superior rectal artery at a low level). The proportion of patients with node-positive disease (Dukes' C) was 40·3 per cent (479 of 1188) in this study, which suggests that low ligation would have led to residual metastases being left in the nodes of a maximum of one-quarter of these patients. Thus, high ligation might save the occasional patient and prove helpful in those who have nodal metastases limited to below the level of the left colic artery by providing a greater margin of safety when the artery, including all the surrounding glands and lymphatics, is excised by a single block dissection; however, these data are inconclusive. The survival benefit of high ligation still remains to be investigated. Likewise, to say that high ligation of the IMA is essential to remove nodes at

station 253 is premature at the present time. Dunphy and Pikula[23] suggested a modified procedure instead of high ligation, in which fatty tissues and nodes were dissected free and excised in the angle between the IMA and aorta, and the artery was ligated below the left colic branch. Comparison of this procedure with high ligation is beyond the scope of this paper.

The results of this study suggest that high ligation of the IMA is beneficial in patients with node-positive disease. An optimal lymphadenectomy, therefore, should include the dissection of tumour-containing nodes. When the operative findings have indicated that high ligation of the IMA should be performed in patients undergoing colorectal cancer resection, several authors have reported the anatomical distribution of nodal metastases along the IMA[4,6,7]. However, intraoperative assessment for the presence of lymph node metastases is not reliable[12]. This uncertainty was demonstrated in the present study as nearly half of the patients with positive station 253 nodal metastases had no metastases in station 252 nodes. Upper lymphatic spread along the IMA was strongly related to the depth of tumour invasion. Both station 252 and 253 nodal metastases occurred more frequently in patients with pT3 and pT4 tumours. In contrast, no station 253 nodal metastases occurred in those with pT1 cancers. Therefore, low ligation may be sufficient for pT1 sigmoid colon or rectal cancers. However, there is no method of accurately assessing the depth of tumour invasion before or during operation. Indeed, by using information on the extent of lymph node involvement and the depth of tumour invasion, it is impossible to decide whether high ligation should be performed for sigmoid colon or rectal cancer. An ill chosen or poorly executed operation may increase the risk of local recurrence and adversely affect survival.

The present results show that high ligation of the IMA can be performed safely and is of therapeutic value in patients with sigmoid colon or rectal cancer who have IMA root node metastases. They also provide indirect evidence that high ligation has a possible beneficial effect on patients with middle-level node metastases along the IMA. These findings indicate that wide resection of the regional mesenteric lymphatics with high ligation of the IMA should usually be performed when operating with curative intent for sigmoid colon or rectal cancer.

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