

## **Optimal lymph node dissection for T3-T4 lower rectal cancer, the so-called “high risk” group: the Japanese experience**

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### **Introduction**

The principal aim of radical surgery for rectal cancer is complete resection of the tumor together with its feeding and lymphatic vessels. There are two types of lymphatic flow from lower rectal cancer: proximal lymphatic flow, toward the root of the inferior mesenteric artery in the mesorectum, and lymphatic flow toward the pelvic sidewall alongside the internal iliac blood vessels beyond the mesorectum.

In order to prevent postoperative local recurrence after resection of rectal cancer, it is important to fully excise all lymphatic tissue around the rectum, leaving no remnants of cancer cells. In the West, the primary goal of rectal surgery is complete resection with free circumferential and distal surgical margins: total mesorectal excision (TME) or tumor-specific mesorectal excision (TSME). T3-T4 lower rectal cancers with full thickness penetration of the rectal wall frequently show regional mesorectal lymph node metastasis and, sometimes, extramesorectal invasion or lateral pelvic node metastasis. Therefore, in the West, patients with T3-T4 lower rectal cancer, the so-called “high risk” group, are typically treated by TME in combination with radiotherapy and chemotherapy. In Japan, on the other hand, surgeons typically carry out extended TME/TSME combined with pelvic side wall node dissection (PSD) in such “high risk” group patients.

The pelvis presents certain anatomical difficulties from the surgical point of view associated with various complications such as bleeding and impotence. However, despite these difficulties, Japanese surgeons have managed to successfully carry out extended node dissection for many years, with the first PSD procedure for rectal cancer being reported by the Japanese surgeon Dr. Kuru in 1940. Unfortunately, this report is only available in Japanese.

Good oncological outcomes may be obtained by optimal dissection techniques. Recently, the incidence of local recurrence of T3-T4 lower rectal cancer after resection has been shown to be 10% or lower in Japan, even when performed without adjuvant radiotherapy. However, important issues remain to be discussed with regard to PSD. While extended node dissection has been found to decrease local recurrence, injury to the autonomic nervous system may sometimes occur. We found that PSD frequently resulted in urinary and sexual dysfunction due to such injury. Furthermore, PSD has been criticized based on the lengthy operation time required and amount of bleeding incurred.

In this report, I would like to describe the current state of knowledge with regard to lymph node metastasis from rectal cancer (site, frequency and clinical impact) based on our experience in Japan. In particular, I would like to discuss PSD with reference to the data accumulated in the Japanese Colorectal Cancer Group study “Research on pelvic side wall dissection”, which was conducted in order to clarify the risk profile for, and clinical impact of, PSD together with the incidence of side wall node metastasis and rates of survival and local recurrence (1).

I believe that the Japanese experience of treatment of “high risk” T3-T4 lower rectal cancer offers useful information on the treatment of this disease. Therefore, I would like to describe surgical treatment for lower T3-T4 rectal cancer in Japan.

## Lower rectal cancer

There is no universal agreement as to what constitutes the lower rectum, and subsequent difficulties in defining lower rectal cancer make a comparison of studies problematic.

According to the latest TNM classification of the International Union Against Cancer (UICC), lower rectal cancer is defined as a tumor with its lower edge at, or less than 6 cm from, the anal verge. The Japanese definition (Japanese Society for Cancer of the Colon and Rectum: Guidelines 2005 for the Treatment of Colorectal Cancer) (2), however, is different, defining the tumor according to anatomical points, rather than measurement, with location categorized according to site of infiltration (usually the center of the lesion). According to the Japanese classification, lower rectal cancer is defined as a tumor that extends below the peritoneal reflection. The Japanese classification is based on the fact that the rectum below the peritoneal reflection contains lymphatic channels extending laterally into the pelvic sidewalls, beyond the mesorectum. Lower rectal cancer defined according to the Japanese classification, however, would undoubtedly also be accepted as a lower rectal cancer in the West.

The Japanese definition may be simple and reproducible, but final classification is based on operative findings.

## Surgical techniques of extended TME+PSD

There is still no consensus on autonomic nerve preservation in PSD. When there is no direct permeation of the cancer to the autonomic nervous system, Japanese surgeons usually perform PSD, taking care to preserve the autonomic nervous system as much as possible. If both the S4 pelvic nerve and peripheral branches are preserved unilaterally, critical complications, such as the need to insert a urine catheter, are avoidable. Severe urinary dysfunction is not usually seen in PSD patients in whom the autonomic nerves have been preserved bilaterally; normal sexual function, however, including ejaculation, is only preserved in 50-60% of such cases, with erectile function alone in 70-80%.

PSD procedures vary from surgeon to surgeon. I would like to describe my own PSD procedure, in which the autonomic nerves are preserved. PSD is commenced after specimen extraction (TME). First, the common iliac artery and vein are exposed. Then, presacral adipose tissue at the front of the bifurcation area is removed from the hypogastric nerve and plexus. Subsequently, the external iliac vessels are exposed. The root of the internal iliac artery is then clarified. Adipose tissue around the obturator nerve is exfoliated from the pelvic sidewall. Dissection is performed from the outside in toward the front of the sciatic nerve. The belly side of the sciatic nerve is interlaced with a network of fine veins, so electric cauterization or ligation is carried out carefully. After dissection of adipose tissue from the sciatic nerve, internal iliac vessels are exposed as far as the origin of the superior vesical artery. Tissue containing lymph nodes located in the obturator space outside the superior vesical artery may be extracted *en block*.

Finally, lymph nodes between the pelvic plexus and internal iliac vessels are dissected. The distal end of the internal iliac vessels is exposed as far as the entrance of the Alcock canal. Small branches of the middle rectal artery penetrating the pelvic plexus are cauterized near the plexus. Piriform muscle can be found behind the internal iliac vessels. The small S3 and S4 pelvic nerves originate only from the inner side of the piriform muscle, and it is necessary to take care not to injure these fine nerve fibers. Blood vessels and pelvic sidewall structures are skeletonized after PSD. The lumbar splanchnic nerves, superior hypogastric plexus, the trunks of the hypogastric nerve, pelvic plexus, and peripheral branches are all preserved (Fig. 1).

*Data analysis from Japanese multi-center study “Research on pelvic side wall dissection”*

In a Japanese multi-center study, the “Research on pelvic side wall dissection”, records were ac-

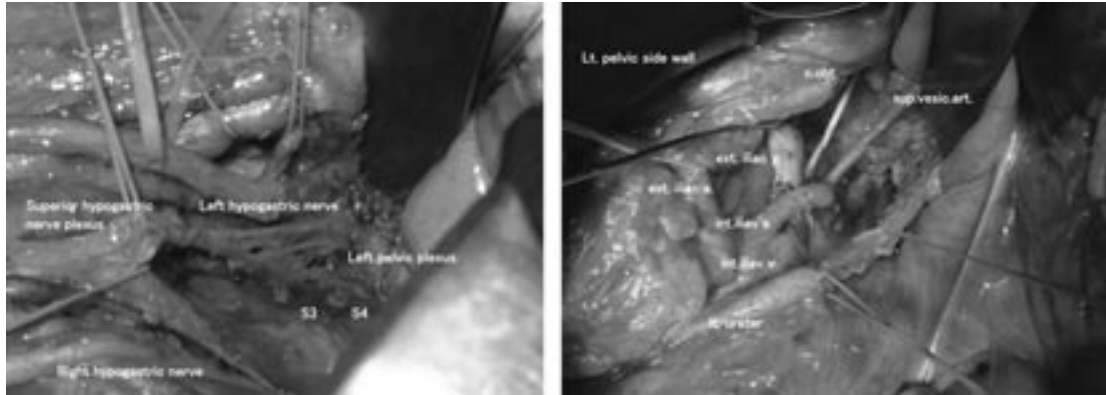


Fig. 1 - Extended pelvic side wall dissection (TME/TSME+PSD).

cumulated on consecutive patients with rectal cancer undergoing curative surgery between January 1991 and December 1998 in 12 leading Japanese hospitals (Aichi Cancer Center Hospital, Tokyo Metropolitan Komagome Hospital, National Defense Medical College Hospital, Tokyo Women's Medical University Hospital, Kurume University Hospital, International Medical Center of Japan, Hirosaki University Hospital, Keio University Hospital, National Cancer Center East, Cancer Institute Hospital, Kinki University Hospital, and Tokyo Medical and Dental University Hospital). The project database contains 2916 consecutive patients with rectal cancer, including 821 patients with T3-T4 lower rectal cancer. Among the 821 patients with T3-T4 lower rectal cancer, 653 patients underwent extended TME (TME/TSME+PSD) (653/821,79.5%). The characteristics of the patients treated by extended TME are shown in Table 1.

*High or low ligation: which is optimal procedure for T3-T4 low rectal cancer?*

Which is optimal, high or low ligation of the inferior mesenteric artery (IMA) for lower T3-T4 rectal cancer? Guideline 2000 of the U.S. recommends low ligation and circumferential mesorectal excision of up to 3 cm distal of the tumor. In Japan, the standard procedure for proximal lymphatic invasion of T3-T4 rectal cancer is lymph node dissection accompanied by high ligation of IMA, and root node IMA dissection, which preserves the left colic artery, is often seen. I usually preserve the left colic artery in operating on rectal cancer in order to prevent ischemic enteritis, and in order to preserve the intestinal tract in operating on a metachronous colorectal cancer.

The frequency of metastasis to each mesorectal node site is shown in Table 2 according to tumor TNM classification. Table 3 shows frequency of mesorectal lymph node metastasis by lymph node site and prognosis. The n-numbers indicate the furthest site of node metastasis from the tumor as follows: n1, peri- or para-rectal node (lymph node station #251); n 2, node metastasis along IMA (lymph

TABLE 1 - CHARACTERISTICS OF PATIENTS WITH T3-T4 LOWER RECTAL CANCER UNDERGOING PELVIC SIDE WALL DISSECTION (PSD).

Characteristics	
Mean±SD age (years)	59.5±10.1
Sex	
M:F	435:217
Wall penetration	
pT3:pT4	603:50
Rectal resection	
LAR:APR:Hartmann	294:336:23
Number of nodes examined	
Mean±SD	46.4±22.8
Median	45.0
Number of positive nodes	
Mean±SD	2.5±4.1
Median	1.0
Adjuvant Radiation Therapy (ART)	
Preop:Postop:Pre+Post	87:19:9

TABLE 2 - INCIDENCE OF MESORECTAL LYMPH NODE METASTASIS IN PATIENTS WITH T3-T4 LOWER RECTAL CANCER.

Wall penetration	No patients (%)	n0 (%)	n1 (%)	n2 (%)	n3 (%)
pT3	553 (100)	272 (49.2)	186 (33.6)	79 (14.3)	16 (2.9)
pT4	43 (100)	20 (46.5)	10 (23.2)	9 (21.0)	4 (9.3)

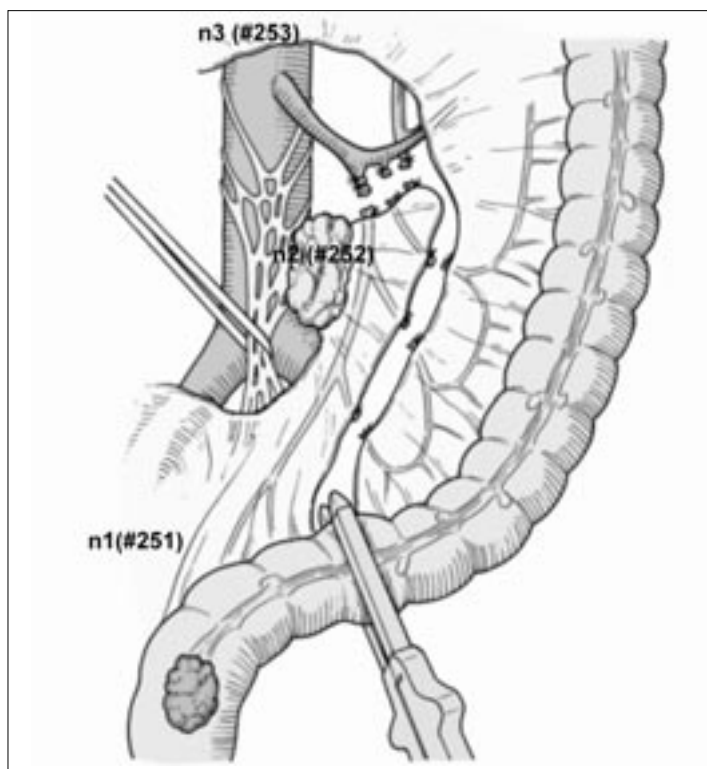


Fig. 2 - Station of mesorectal lymph node (Japanese Society for Cancer of the Colon and Rectum)

TABLE 3 - SURVIVAL OF T3-T4 LOWER RECTAL CANCER PATIENTS WITH MESORECTAL LYMPH NODE (LN) METASTASIS (TOTAL PATIENTS n=593).

Mesenteric LN metastasis	No patients (%)	5-yr OS (%)	5-yr RFS (%)	% improvement 5-yr survival rate
n0	292 (49.2)	84.5	81.4	-
n1	196 (33.0)	66.4	58.4	21.8
n2	86 (14.5)	52.7	47.8	7.8
n3	20 (3.3)	36.9	26.3	1.2

\* Improvement of 5-year survival rate = rate of positive lymph nodal metastases x 5-year survival rate in patients with positive lymph nodal metastases.

node station #252); and n3, node located between root of IMA and root of left colic artery (lymph node station #253) (Fig. 2). Generally, lymph node invasion takes place sequentially, commencing from near the tumor, and then moving further away. Skip lymph node metastasis to #252, jumping over #251, and that to #253, jumping over #252, is very rare. In my own experience, skip metastases to #253 over #252 occupied only 1% (2/182), and skip metastases to #252 over #251 occurred in only 2% of cases (4/182). The 5-year survival rate after curative surgery by degree of lymph node metastasis was 83.9, 73.7, 58.4 and 37.0% for n0, n1, n2, and n3, respectively. IMA root nodal dissection would improve the 5-year survival rate of patients with pT3-T4

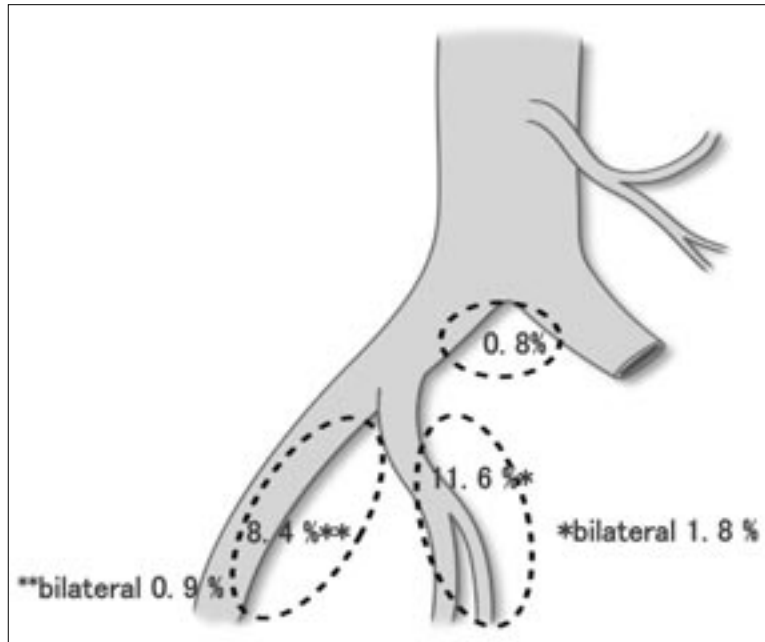


Fig. 3 - Site of lateral lymph node metastasis in patients with T3-T4 lower rectal cancer.

lower rectal cancer by 1.2 % (“improvement of 5-year survival rate” = “rate of positive lymph node metastases” × “5-year survival rate of patients with positive lymph node metastases”).

The survival benefit of #253 node dissection of the IMA is small. It is believed that #253 node dissections are useful for determining staging. Furthermore, it is useful to dissect as far as the vicinity of the origin of the IMA in order to ensure complete dissection of the #252 lymph node.

*Efficacy of PSD: frequency of side wall node metastasis and prognosis after PSD*

The frequency of side wall node metastasis of T3-T4 lower rectal cancer is shown in Table 4. Positive node rate according to site on pelvic sidewall is shown in Figure 3. Positive lateral lymph nodes were found in 18.1% of patients. Lymph node metastases occurred more frequently in patients with pT4 lower rectal cancer. The data analysis revealed that the frequency rate for the sidewall node was 16.7% in T3, and 34% in T4.

Lymph node metastases occurred more frequently in patients with pT4 lower rectal cancer. The 5-year survival and relapse-free survival rates in patients with pelvic side wall lymph node involvement were 42.8% and 34.8%, respectively. PSD improved the 5-year survival rate in patients with pT3-T4 lower rectal cancer by 7.7% (improvement of 5-year survival rate = rate of positive lymph nodal metastases × 5-year survival rate in patients with positive lymph nodal metastases) (Table 5).

PSD should be indicated for patients with T3-T4 lower rectal cancer due to the greater probability of positive lateral lymph nodes and its survival benefit in patients with pelvic side wall lymph node metastases.

*Which is optimal, extended TME (TME+PSD) or TME+adjuvant radiotherapy?*

In patients with rectal cancer, overall locoregional recurrence rate varies widely, from 3 to 33%,

TABLE 4 - INCIDENCE OF LATERAL LYMPH NODE METASTASIS IN PATIENTS WITH T3-T4 LOWER RECTAL CANCER.

Wall penetration	No patients (%)	NO (%)	YES (%)
pT3	603(100)	502(83.2)	101(16.8)
pT4	50(100)	33(66.0)	17(34.0)

TABLE 5 - SURVIVAL IN T3-T4 LOWER RECTAL CANCER PATIENTS WITH MESORECTAL LYMPH NODE (LN) METASTASIS (TOTAL PATIENTS n = 65).

Lateral LN metastasis	No patients (%)	5-yr OS (%)	5-yr RFS (%)	5-yr local RFS (%)	% improvement 5-yr survival rate*
NO	535 (81.9)	74.7	69.7	88.5	-
YES	118 (18.1)	42.8	34.8	72.6	7.7

\* Improvement of 5-year survival rate = rate of positive lymph nodal metastases  $\times$  5-year survival rate in patients with positive lymph nodal metastases.

whereas total mesorectal excision (TME) has consistently shown an approximately 10% locoregional rate (4, 5).

In many institutions, TME has yielded a low rate of local failure. However, the local recurrence rate in patients with lower rectal cancer remains high. The efficacy of TME requires reevaluation with respect to tumor location, depth of invasion, mesorectal lymph node involvement, adjuvant treatment and strict definition of local recurrence.

In patients treated with TME alone without extended PSD, microscopic involvement of the circumferential margin and lateral pelvic lymph nodes beyond the mesorectum may be one cause of local failure.

In Japan, PSD is often performed in lower rectal cancer surgery without resort to adjuvant radiotherapy. PSD usually involves a longer surgery time and greater blood loss than TME alone. Recently, PSD has been performed in selected patients with T3-T4 lower rectal cancer in Japan.

Efforts have been made to utilize a range of imaging techniques in the detection of pelvic sidewall node metastases in order to identify high risk patients, and the use of the end-rectal coil in MRI, in particular, has improved our ability to do so. However, no imaging technique can reveal all lateral node metastases. Therefore, it is difficult to determine whether PSD is appropriate for patients with lower rectal cancer preoperatively.

I would like to compare extended TME+PSD and TME with adjuvant radiotherapy strategy for T3-T4 lower rectal cancer from the viewpoint of control of local recurrence and complications. The postoperative local recurrence rate in patients with T3-T4 lower rectal cancer was 12% in a group of Japanese patients who underwent TME+PSD without radiotherapy. If PSD had been not performed in patients with sidewall node metastasis, those patients would have developed local recurrence. Therefore, the local recurrence rate in cases without PSD was estimated to be 26% in the Japanese data analysis (data not shown).

The postoperative local recurrence rate for lower rectal cancers located less than 10 cm from the AV was 26-27% by surgery alone and 9-10% by surgery with adjuvant radiotherapy among cases registered in a Swedish trial (5). The rate of local recurrence after TME alone in lower rectal cancer in a Swedish trial was very similar to the estimated local recurrence rate by TME alone from our data analysis. Moreover, in a clinical trial carried out by Fazio et al. (6) comparing TME+adjuvant radiotherapy with TME alone for T3 lower rectal cancer, the TME group showed a local recurrence rate of 24% in the N1 group (n=135) and 12% in the N0 group (n=122). Our data analysis suggested that 25% of T3 lower rectal cancer patients with mesorectal node metastasis (N+) would have pelvic sidewall node metastasis (data not shown). The rate of local recurrence after TME alone in T3 lower rectal cancer patients in the Fazio trial was very similar to the estimated rate of pelvic sidewall node metastasis from our Japanese data analysis. Of course, not all local recurrences involve sidewall node metastasis. The results of the Swedish and Fazio trials suggest that the local control effects of adjuvant radiotherapy and PSD are almost equivalent in patients with similar rectal tumors in terms of site, extent of invasion and mesorectal node metastasis. This means that TME with PSD and TME with pre-or postoperative adjuvant radiotherapy for high risk lower rectal cancer have the same effect on locoregional control. In a recent Japanese trial comparing PSD with preoperative radiotherapy, no differences were found in locoregional recurrence or survival, although genitourinary dysfunction showed an increase in the PSD group (7).

Certainly, urinary dysfunction and, in particular, sexual dysfunction are encountered in PSD at high frequency. However, urinary, sexual, and defecatory dysfunction is also encountered after

radiotherapy. According to a report on late period complications in a Dutch trial carried out recently (8), anal functional disorders (such as incontinence and anal bleeding) and sexual dysfunction (especially, compromised ejaculation ability) were found to occur often after radiotherapy. Moreover, medical economics, in terms of the time burden associated with radiotherapy, cannot be disregarded. Recently, Hashiguchi et al reported that short-course radiotherapy was insufficient to control lateral pelvic node metastasis (9).

Surgical treatment for "high risk" T3-T4 lower rectal cancer is a major challenge. However, although by no means easy for a relatively inexperienced surgeon, for one with greater experience and an in-depth knowledge of the anatomy of the pelvic cavity, this procedure may still offer a safe option. Since the surgeon's most important task is locoregional control by tumor resection, PSD should be positively performed in high risk patients after obtaining informed consent with regard to the potential ensuing obstacles to reproductive function. I believe that patients with high risk lower rectal cancer should be offered the option of TNE+PSD or TME+ radiotherapy after appropriate explanation of the risks involved.

## Conclusion

In patients with T3-T4 lower rectal cancer, the incidence of metastasis to root nodes is low, and IMA root nodal dissection (high ligation) offers few advantages due to poor prognosis. On the other hand, PSD should be indicated for patients with T3-T4 lower rectal cancer due to the high probability of positive sidewall nodes. Pelvic side wall dissection offers a potential survival benefit for T3-T4 lower rectal patients with lateral lymph node metastasis. However, urinary and sexual dysfunction is encountered at high frequency with PSD. Therefore, patients with high risk lower rectal cancer should be offered the option of TNE+PSD or TME+ radiotherapy after appropriate explanation of the risks involved.

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