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RAPID COMMUNICATION

Risk factors for lymph node metastasis and evaluation of reasonable surgery for early gastric cancer

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Abstract

AIM: To give the evidence for rationalizing surgical therapy for early gastric cancer with different lymph node status.

METHODS: A series of 322 early gastric cancer patients who underwent gastrectomy with more than 15 lymph nodes retrieved were reviewed in this study. The rate of lymph node metastasis was calculated. Univariate and multivariate analyses were performed to evaluate the independent factors for predicting lymph node metastasis.

RESULTS: No metastasis was detected in No.5, 6 lymph nodes (LN) during proximal gastric cancer total gastrectomy, and in No.10, 11p, 11d during for combined resection of spleen and splenic artery and in No.15 LN during combined resection of transverse colon mesentery. No.11p, 12a, 14v LN were proved negative for metastasis. The global metastastic rate was 14.6% for LN, 5.9% for mucosa, and 22.4% for submucosa carcinoma, respectively. The metastasis in group Ⅱ was almost limited in No.7, 8a LN. Multivariate analysis identified that the depth of invasion, histological type and lymphatic invasion were independent risk factors for LN metastasis. No metastasis from distal cancer (≤ 1.0 cm in diameter) was detected in group Ⅱ LN. The metastasis rate increased significantly when the diameter exceeded 3.0 cm. All tumors (≤ 1.0 cm in diameter) with LN metastasis and mucosa invasion showed a depressed macroscopic type, and all protruded carcinomas were > 3.0 cm in diameter.

CONCLUSION: Segmental/subtotal gastrectomy plus D_1/D_1 + No.7 should be performed for carcinoma (≤ 1.0 cm in diameter, protruded type and mucosa invasion). Subtotal gastrectomy plus D_2 or D_1 + No.7, 8a, 9 is the most rational operation, whereas No.11p, 12a, 14v lymphadenectomy should not be recommended routinely for poorly differentiated and depressed type of submucosa carcinoma (> 3.0 cm in diameter). Total gastrectomy should not be performed in proximal, so does combined resection or D_2^+/D_3 lymphadenectomy.

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Key words: Lymph node; Metastasis; Surgery; Early gastric cancer

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INTRODUCTION

Gastric cancer is still one of the important causes of cancer-related death in China. Although early gastric cancer accounts for less than 10% of gastric cancers, excellent outcome of surgery has been reported, with a 5-year survival rate higher than 90%[1-3]. In the past 20 years, most surgeons considered D_2 lymphadenectomy the standard and optimal surgical procedure for patients with early gastric cancer. Even total gastrectomy and D_3 lymphadenectomy with combined resection of other organs have been used to achieve curative (R_0) resection[3-9]. The lymph node metastasis rate of early gastric cancer is reported to be 11%-18% and 70%-80% patients will undergo over-surgery with D_2 lymphadenectomy[1,4,8,9]. Consequently, investigating the risk factors for lymph node metastasis is the key to rational surgery of early gastric cancer, which may improve the 5-year survival rate of patients and their quality of life. This study was to retrospectively analyze the location, frequency, degree of and risk factors for lymph node metastasis in 322 patients with early gastric cancer, in order to rationalize surgical therapy.

MATERIALS AND METHODS

Patients

Between February 1972 and August 2006, a consecutive series of 322 early gastric cancer patients underwent

Table 1 Site and frequency of lymph node metastasis of cancer in the lower and middle thirds of stomach

The lower third of the stomach	Frequency of LNM		The middle third of the stomach	Frequency of LNM	
	Possitive	%		Possitive	%
Group 1			Group 1		
No.3	12	4.9	No.1	3	4.8
No.4	16	6.5	No.3	6	9.7
No.5	3	1.2	No.4	0	0.0
No.6	14	5.7	No.5	1	1.6
			No.6	1	1.6
Total	35	14.3	Total	8	12.9
Group 2			Group 2		
No.1	1	0.4	No.7	3	4.8
No.7	13	5.3	No.8a	1	1.6
No.8a	7	2.9	No.9	0	0.0
No.9	2	0.8	No.11p	0	0.0
No.11p	0	0.0	No.12a	0	0.0
No.12a	0	0.0			
No.14v	0	0.0			
Total	18	7.3	Total	4	6.5

LNM: Lymph node metastasis; No.1: Right paracardial LN; No.3: LN along the lesser curvature; No.4: LN along the greater curvature; No.5: suprapyloric LN; No.6: Infrapyloric LN; No.7: LN along the left gastric artery; No.8a: LN along the common hepatic artery (anterosuperior group); No.9: LN around the celiac artery; No.11p: LN along the proximal splenic artery; No.12a: LN in the hepatoduodenal ligament (along the hepatic artery); No.14v: LN along the superior mesenteric vein.

gastrectomy at the Department of Oncologic Surgery, First Affiliated Hospital, China Medical University. The patients (242 men and 80 women) ranged in age from 19 to 80 (53.8 ± 12.3) years participated in the study. Early gastric cancer was located in the lower third of stomach (L/LM) of 145 patients, in the middle third (M/ML/MU) of 14 patients, in the upper third (U/UM) of 11 patients, and in whole stomach (UML) of 4 patients. A total of 292 patients underwent distal gastrectomy, 10 proximal gastrectomy, 20 total gastrectomy, 2 combined resection of spleen, and 3 combined resection of transverse colon mesentery. D_1 lymphadenectomy was performed in 57 patients; D_1 + No.7 in 58 patients; D_1 + No.7, 8a, 9 in 63 patients; D_2 in 107 patients; and D_2^+ or D_3 in 37 patients. The methods of pathology diagnosis, lymph node grouping and surgery have been described previously[10].

Pathology

Serial section of specimens was performed for an accuracy pathological diagnosis. Mucosa carcinoma was diagnosed in 152 patients and submucosa carcinoma in 170 patients based on the depth of invasion. Protruded type was found in 23 patients, flat type in 38 patients, and depressed type in 263 patients, respectively in the light of macroscopic appearance. The tumor diameter ranged from 0.4 to 14.0 (3.2 ± 1.8) cm. Well or moderately differentiated tumor was found in 142 patients, and poorly differentiated tumor in 180 patients according to their histological type. Mass type was observed in 102 patients, nest type in 91 patients and diffused type in 129 patients, respectively, based on the histological growth pattern. Lymphatic vessel invasion occurred in 19 patients.

Statistical analysis

All data were analyzed by SPSS11.5. The correlation between clinicopathological factors and nodal involvement was evaluated by univariate analysis. Multivariate analysis was performed to evaluate the independent factors for predicting lymph node metastasis. $P < 0.05$ was considered statistically significant.

RESULTS

Evaluation of lymphadenectomy

Five patients underwent combined resection of other organs due to misdiagnosis as advanced gastric carcinoma. Depressed type of mucosa and submucosa carcinoma was diagnosed in 2 and 3 patients, respectively. Proximal gastric cancer without metastasis in No.10, 11p, 11d lymph nodes was diagnosed in 2 patients undergoing combined resection of spleen and splenic artery. Distal gastric cancer without metastasis in No.15 lymph node was diagnosed in 3 patients undergoing combined resection of transverse colon mesentery. No.5, 6 lymph nodes were negative in 20 patients with proximal gastric cancer after total gastrectomy.

Metastasis of distal gastric cancer was found in 2 out of the 37 patients undergoing extended lymphadenectomy (> D_2). Depressed type of mucosa and submucosa carcinoma was found in the 2 patients. Metastasis of group I lymph nodes was detected both in 285 patients with middle and distal gastric cancer who underwent ≤ D_2 lymphadenectomy. The detection rate was 12.9% and 14.3%, respectively. A frequent metastasis of No.7, 8a lymph nodes (6.5%-8.2%) and an occasional metastasis of No.9 lymph nodes were also found. No metastasis was detected in No.11, 12a, 14v lymph nodes (Table 1).

Relationship between frequency of lymph node metastasis and location of focus

The number of retrieved lymph nodes in all patients was more than 15, ranging from 15 to 75 (median, 16). Lymph node metastasis was detected in 47 patients (14.6%), and the number of metastatic lymph nodes ranged from 1 to 16 (median, 2). Of the patients with lymph node metastasis, 33 were male (13.6%), 14 female (17.5%). Distal gastric cancer was diagnosed in 38 patients (15.5%), middle gastric cancer in 9 (14.5%), protruded type in 3 patients (14.3%), flat type in 4 patients (10.5%),and depressed type in 40 patients (15.2%). The diameter of tumor was ≤ 1.0 cm in 5 patients (19.5%), 1.1-2.0 cm in 13 patients (11.2%), 2.1-3.0 cm in 6 patients (10.0%), > 3.0 cm in 23 patients (19.2%). Mucosa carcinoma was found in 9 patients (2.9%), submucosa carcinoma in 38 patients (22.4%), poorly differentiated carcinoma in 35 patients (19.4%), well or moderately differentiated in 12 patients (8.5%), mass type in 15 patients (14.7%), nest type in 12 patients (13.2%), diffused type in 20 patients (15.5%), negative lymphatic invasion in 36 patients (57.9%), and positive lymphatic invasion in 11 patients (11.9%).

Of the 245 patients with distal gastric cancer, 35 had metastasis in group I lymph nodes (14.3%), and 18 in group Ⅱ lymph nodes (7.3%). Metastasis was detected in all group

Table 2 Comparison of clinicopathological features between patients with and without lymph node metastasis

Factors	Node negative	Node positive	*P* value
Dissected nodes (mean ± SD)	19.3 ± 7.5	20.8 ± 6.9	0.188
Age, yr (mean ± SD)	53.9 ± 12.1	52.9 ± 13.2	0.606
Tumor maximum diameter (cm, mean ± SD)	3.1 ± 1.8	3.5 ± 1.8	0.197
Gender			
Male	209	33	
Female	66	14	0.465
Tumor location			
Upper	11	0	
Middle	53	9	
Lower	207	38	0.435
Total	4	0	
Depth of invasion			
Mucosa	143	9	
Submucosa	132	38	< 0.001
Histological type			
Differentiated	130	12	
Undifferentiated	145	35	0.007
Macroscopic type			
Protruded	18	3	
Flat	34	4	0.746
Depressed	223	40	
Growth manner			
Mass	87	15	
Nest	79	12	0.891
Diffuse	109	20	
lymphatic invasion			
Negative	267	36	
Positive	8	11	< 0.001

Differentiated: Papillary and tubular adenocarcinoma; Undifferentiated: Poorly differentiated adenocarcinoma and signet-ring cell carcinoma; Protruded: Ⅰ and Ⅱa; flat: Ⅱb; depressed: Ⅱc and Ⅲ.

Table 3 Logistic regression analysis for variables associated with lymph node metastasis in EGC

Explanatory variables	Odds ratio	95% CI	*P* value
Depth of invasion	3.67	1.62-8.30	0.002
Histological type	3.39	1.39-8.27	0.007
Lymphatic invasion	8.41	2.86-24.74	< 0.001
Tumor maximum diameter	1.23	1.0-1.49	0.042
Gender	1.10	0.46-2.21	0.981
Age	0.99	0.97-1.03	0.726
Tumor location	0.60	0.29-1.23	0.161
Growth manner	0.58	0.26-1.30	0.186
Macroscopic type	1.14	0.56-2.34	0.715

CI: Confidence interval. Depth of invasion, histological type, lymphatic invasion and tumor maximum diameter are the independent risk factors correlated with lymph node involvement.

Ⅰ lymph nodes with a frequency of 5.7% for No.6, 6.5% for No.4, 4.9% for No.3, and 1.2% for No.5, respectively. In group Ⅱ lymph nodes, the most frequent metastasis was detected in No.7 lymph nodes (5.3%) and No.8a lymph nodes (2.9%), and less frequent metastasis in No.9 lymph nodes (0.8%), No.1 lymph nodes (0.4%). Metastasis of group Ⅲ lymph nodes was detected in only 2 patients.

Of the 62 patients with middle gastric cancer, 8 had metastasis of group Ⅰ lymph nodes (12.9%), and 4 had metastasis of group Ⅱ lymph nodes (6.5%). The rate of metastasis of group Ⅰ lymph nodes was 9.7% for No.3, 4.8% for No.1, 1.6% for No.5, and 1.6% for No.6, respectively. Metastasis of No.7 (4.8%) and No.8a (1.6%) lymph nodes was detected in group Ⅱ lymph nodes. No lymph node metastasis was detected in the 11 patients with proximal gastric cancer.

Risk factors correlated with lymph node involvement

In this series, the mean number of retrieved lymph nodes was 19.3 ± 7.5 in patients without lymph node metastasis, and 20.8 ± 6.9 in patients with lymph node metastasis. The difference was not significant ($F = 1.741$, $P = 0.188$). The univariate analysis showed that three variables were significantly indicative of lymph node metastasis: depth of invasion, histological type, and lymphatic invasion ($P < 0.001$). The lymph node metastasis rate of poorly differentiated submucosa carcinoma with positive lymphatic invasion was significantly higher than that of well differentiated mucosa carcinoma with negative lymphatic invasion (Table 2).

The multivariant analysis showed that all the variables (depth of invasion, histological type, and lymphatic invasion) remained significant, indicating that the independent risks were correlated with lymph node involvement. The lymph node metastasis of submucosa carcinoma was 3.7 times higher than that of mucosa carcinoma. The lymph node metastasis of poorly differentiated carcinoma was 3.4 times higher than that of well differentiated carcinoma. The positive lymphatic invasion was 8.4 times higher than that of negative lymphatic invasion. The maximum diameter of the tumor was also an important variable correlated with lymph node involvement (OR = 1.23, $P = 0.042$), the rate of lymph node metastasis was associated with the maximum tumor diameter (Table 3).

Relationship between lymph node metastasis and clinicopathological factors for distal gastric cancer

Metastasis of distal gastric cancer hardly went beyond group Ⅰ lymph nodes when the maximum tumor diameter was ⩽ 1.0 cm. Corresponding to the increased maximum diameter, the rate of metastasis in group Ⅱ lymph nodes was increased, but often limited in No7, 8a lymph nodes. Only when the maximum tumor diameter was > 3.0 cm, could metastasis of No.1 and 9 lymph nodes be detected. Compared with protruded type of carcinoma, in which metastasis could only be detected in group Ⅰ lymph nodes, depressed type of carcinoma often had combined metastasis in both group Ⅰ and Ⅱ lymph nodes, and the number of metastasis lymph nodes would increase significantly. Metastasis of mucosa carcinoma was detected in all group Ⅰ lymph nodes. Metastasis of poorly differentiated and depressed types of mucosa carcinoma in No.1 lymph nodes was detected in only 1 patient, whose tumor diameter was > 3.0 cm. Metastasis of submucosa carcinoma was detected in both group Ⅰ and Ⅱ lymph nodes, and the rate of lymph node metastasis was significantly higher than that of mucosa carcinoma ($P < 0.01$). Metastasis of poorly and well differentiated carcinoma was detected in group Ⅰ and Ⅱ lymph nodes, but the metastasis rate of poorly differentiated

Table 4 Depth of invasion, histological type, macroscopic type, lymphatic penetration of lymph node metastasis and tumor maximum diameter in the lower third of stomach

Factors	Group 1 metastasis (person)						Group 2 metastasis (person)					
	No.3	No.4	No.5	No.6	Total	*P* value	No.1	No.7	No.8a	No.9	Total	*P* value
Tumor maximum diameter (cm)												
≤ 1.0	1	0	0	3	4		0	0	0	0	0	
1.1-2.0	4	4	2	4	11		0	3	3	0	5	
2.1-3.0	0	2	1	0	3		0	1	0	0	1	
> 3.0	7	10	0	7	17	0.143	1	9	4	2	12	0.018
Histological type												
Diff	4	4	0	4	8		0	2	0	1	2	
Undiff	8	12	3	10	27	0.025	1	11	7	1	16	0.006
Depth of invasion												
M	1	4	2	3	9		1	0	0	0	1	
Sm	11	12	1	11	26	0.010	0	13	7	2	17	< 0.001
Growth manner												
Mass	5	5	0	5	10		0	4	3	1	7	
Nest	3	3	2	2	8	0.669	0	3	2	1	4	0.689
Diffuse	4	8	1	7	17		1	6	2	0	7	
Macroscopic type												
Protruded	0	2	0	0	2		0	0	0	0	0	
Flat	1	2	0	1	3		0	2	0	0	2	
Depressed	11	12	3	13	30	0.819	1	11	7	2	16	0.501
Lymphatic invasion												
Negative	10	13	2	11	27		1	8	6	2	13	
Positive	2	3	1	3	8	< 0.001	0	5	1	0	5	< 0.001

Diff: Differentiated histological type; Undiff: Undifferentiated histological type; M: Mucosa; Sm: Submucosa.

carcinoma was significantly higher than that of well differentiated carcinoma ($P < 0.05$). The metastasis rate of positive lymphatic invasive carcinoma was also significantly higher than that of negative lymphatic invasive carcinoma ($P < 0.01$) (Table 4).

DISCUSSION

Since 1980's, D_2 lymphadenectomy has been widely accepted as the standard surgery for early gastric cancer, especially for submucosa carcinoma. However, it was reported that D_2 lymphadenectomy does not increase the long-term survival of patients, compared with D_1 or D_1^+ lymphadenectomy[7-9,11]. Since lymph node metastasis remains one of the most important predictors for survival, reduction in lymphadenectomy will probably result in residue of metastatic lymph nodes. Unnecessarily extended resection will induce a series of complications, which also result in a poor quality of life. Thus, it is important to standardize the optimal extent of lymph node dissection by investigating lymph node metastasis of early gastric cancer.

In the present study, total gastrectomy for carcinoma in the upper third of stomach was selected according to the status of No.5 and 6 lymph nodes. Metastasis was not detected in all proximal gastric cancer patients after total gastrectomy. Considering the complications after total gastrectomy, it was not used as a routine operation for proximal early gastric cancer. Furthermore, metastasis was not detected in No.10, 11p, 11d lymph nodes after combined resection of spleen or splenic artery and in No.15 lymph nodes after combined resection of transverse colon mesentery. Therefore, we conclude that combined resection of other organs should not be performed in early gastric cancer. In our study, most patients undergoing combined resection were due to adhesion of serosa and transverse colon mesentery or due to inflammatory swelling of inflammatory splenic hilum lymph nodes. Thus, estimating the depth of invasion accurately is the key to optimal surgery. Endoscopic ultrasonography and three-dimensional spiral CT (3DCT) provide more accurate information on the depth of invasion. It was reported that 70%-80% of early gastric cancers can be diagnosed by endoscopic ultrasonography combined with three-dimensional CT[12-14].

Whether D_2 lymphadenectomy for early gastric cancer should be performed remains controversial. Many researchers consider D_1 + No.7, 8a or D_1 + No.7, 8a, 9 lymphadenectomy as the standard operation for most of early gastric cancers[15-17]. In our series, no metastasis of middle and distal gastric cancer was detected in No. 11p, 12a, 14v lymph nodes, suggesting that neither dissection of No. 11p, 12a, 14v lymph nodes nor D_2^+/D_3 lymphadenectomy is necessary for distal early gastric cancer.

It was reported that the lymph node metastasis rate is 0%-3% for mucosa carcinoma and 20% for submucosa carcinoma. It has been shown that 9%-16% of metastatic lymph nodes are detected in group Ⅰ, 4%-6% in group Ⅱ, and 0.3%-1% in group Ⅲ[16-18]. In this study, the metastasis rate in group I and Ⅲ lymph nodes is consistent with the reported data. The metastasis rate in group Ⅱ was 7.3% for distal cancer and 6.5% for middle cancer, higher than that in former studies.

It has been widely accepted that the status of lymph node involvement is closely correlated with the depth of invasion, but the relationship between metastasis and focus diameter, histological type and macroscopic type is still controversial[8,16,17,19-21]. Kunisaki *et al*[17] reported that mucosa carcinoma (> 3.0 cm in diameter) has a

higher lymph node involvement, while there is no distinct correlation between the diameter, macroscopic type, histological type and metastasis of submucosa carcinoma. Shimoyama *et al*[16] found that the metastasis rate for intestinal submucosa carcinoma (≤ 1.5 cm in diameter) and diffused submucosa carcinoma r (≤ 1.0 cm in diameter) is very low (3%), and limited in group I lymph nodes. If the diameter went beyond the former cut-point, the rate of metastasis would increase significantly and No.7, 8a, 9 lymph nodes (2.3%) could be detected even in group Ⅱ lymph nodes. Gotoda *et al*[20] reported that lymph node metastasis of well differentiated mucosa carcinoma (≤ 3.0 cm in diameter) is seldom detected. Whereas lymph node metastasis of submucosa carcinoma (> 3.0 cm in diameter) with positive lymphatic invasion increase significantly.

In our study, no metastasis of distal gastric cancer (≤ 1.0 cm in diameter) with mucosa invasion was detected in group Ⅱ lymph nodes. The rate of metastasis in group Ⅱ lymph nodes significantly increased when the tumor diameter was > 3.0 cm. All the carcinomas (≤ 1.0 cm in diameter and/or mucosa invasion) with lymph node involvement showed depressed macroscopic type. The diameter of protruded carcinoma with lymph node involvement was > 3.0 cm. Multivariate analysis showed that the depth of invasion, histological type and lymphatic penetration were independent risk factors for lymph node metastasis and the maximum diameter was also an important factor. Our study also revealed the relationship between metastasis of distal gastric cancer in group Ⅱ lymph nodes and the diameter, histological type, depth of invasion and lymphatic invasion of the tumor. The rate of involved lymph nodes significantly increased compared with poorly differentiated, sub-mucosa carcinoma and positive lymphatic invasion, suggesting that the following high risk factors for lymph node metastasis of distal gastric cancer in group Ⅱ lymph nodes are tumor diameter > 3.0 cm, depressed type, poorly differentiated submucosa carcinoma and positive lymphatic invasion. Standard D_2 lymphadenectomy should be performed to achieve curative (R_0) resection in such patients.

In summary, selection of reasonable surgery for early gastric cancer should be based on the pathobiologic behaviour of the tumor. Segmental/subtotal gastrectomy plus D_1/D_1 + No.7 lymphadenectomy should be performed for carcinoma (≤ 1.0 cm in diameter, protruded type and mucosa invasion). Subtotal gastrectomy plus D_2 or D_1 + No.7, 8a, 9 lymphadenectomy is the most rational operation for poorly differentiated and depressed type of submucosa carcinoma (> 3.0 cm in diameter), whereas No.11p, 12a, 14v lymphadenectomy should not be performed routinely. Total gastrectomy should not be performed for proximal gastric cancer. Combined resection of other organs or D_2^+/D_3 lymphadenectomy should always be avoided.

COMMENTS

Background

Since 1980's, D_2 lymphadenectomy has been widely accepted as the standard surgery for early gastric cancer, especially for submucosa carcinoma. Even total gastrectomy and D_3 lymphadenectomy with combined resection of other organs have been used to achieve curative (R_0) resection. However, it was reported that application of extended surgery does not reasonably increase the long-term survival of patients.

Research frontiers

It has been widely accepted that the status of lymph node involvement is closely correlated with the depth of invasion, but the relationship between metastasis and diameter of focus, histological type and macroscopic type is still controversial. Since lymph node metastasis remains one of the most important predictors for survival, reduction in lymphadenectomy will probably result in residue of metastatic lymph nodes. Unecessarily extended resection will induce a series of complications, which also result in a poor quality of life.

Innovations and breakthroughs

The results of this study show that depth of invasion, histological type and lymphatic invasion are independent risk factors for lymph node metastasis. There is a relationship between the pathobiologic behavior of tumor and reasonable surgery for early gastric cancer.

Applications

With the knowledge of the risk factors and rules of lymph node metastasis, clinical doctors can select surgery for early gastric cancer more reasonably.

Terminology

D lymphadenectomy: Lymph node dissection according to the Japanese Gastric Cancer Association (JGCA) criteria. Lymph node dissection is divide into D_1 lymphadenectomy, D_2 lymphadenectomy and D_3 lymphadenectomy.

Peer review

The authors rationalized surgical therapy for early gastric cancer with different lymph node status and suggest that segmental/subtotal gastrectomy plus D_1/D_1 + No.7 should be performed for carcinoma (≤ 1.0 cm in diameter, protruded type and mucosa invasion). Subtotal gastrectomy plus D_2 or D_1 + No.7, 8a, 9 is the most rational operation for poorly differentiated and depressed type of submucosa carcinoma (> 3.0 cm in diameter), whereas No.11p, 12a, 14v lymphadenectomy should not be recommended routinely. Total gastrectomy or D_2^+/D_3 lymphadenectomy should not be performed in proximal and combined resection.

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