

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Transanal endoscopic microsurgery for rectal neoplasms: experience of 300 consecutive cases

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/100736> since

Published version:

DOI:10.1007/DCR.0b013e3181b14d2d

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

Diseases of the Colon & Rectum 52(11),2009, DOI: 10.1007/DCR.0b013e3181b14d2d

The definitive version is available at:

La versione definitiva è disponibile alla URL:

<http://journals.lww.com/dcrjournal/pages/articleviewer.aspx?year=2009&issue=11000&article=00003&type=abstract>

Transanal Endoscopic Microsurgery for Rectal Neoplasms: Experience of 300 Consecutive Cases

Allaix, Marco Ettore M.D.; Arezzo, Alberto M.D.; Caldart, Mario M.D.; Festa, Federico M.D.; Morino, Mario M.D.

Author Information

Center for Minimally Invasive Surgery, Dipartimento di Discipline Medico Chirurgiche, Università di Torino, Torino, Italy

Abstract

PURPOSE: Abdominal resection for rectal neoplasms is associated with significant morbidity. Local excision with retractors can be proposed only for distal rectal lesions. With this retrospective review of our prospective series of transanal endoscopic microsurgery procedures, we wanted to verify the advantages of local treatment in terms of disease recurrence and complication rates.

METHODS: Indications for transanal endoscopic microsurgery were adenoma, early carcinoma, rectal ulcers, carcinoid tumors, gastrointestinal stromal tumors, and leiomyosarcoma apparently located in the extraperitoneal rectum. We analyzed operating time, morbidity and mortality rates, length of hospital stay, staging discrepancy, recurrence rate, and oncological outcome.

RESULTS: From January 1993 to January 2007, 300 patients underwent transanal endoscopic microsurgery at our institution. The mean operating time was 66 minutes. The peritoneum was inadvertently opened in 13 cases. The overall morbidity rate was 7.7%. The mean hospital stay was five days. Histology demonstrated cancer in 90 patients. At a mean follow-up of 60 months, the recurrence rate was zero in pT1, 24% in pT2, and 50% in pT3. The overall estimated five-year survival rate was 87%, and the disease-free survival rate was 82%.

CONCLUSIONS: Transanal endoscopic microsurgery is safe and effective in the treatment of adenoma and pT1 carcinoma; it carries a lower morbidity than conventional surgery and a recurrence rate comparable to that of conventional surgery.

KEY WORDS: Transanal endoscopic microsurgery; Rectal adenoma; Rectal adenocarcinoma

The rectum is a challenging district for surgeons due to limited access and maneuverability. Although advances in conventional surgery have led to a broader choice of sphincter-saving procedures, definitive colostomy is still necessary in 10% to 30%¹ of cases. Also, postoperative morbidity and mortality rates remain high,² including urogenital dysfunction.³ Transanal excision has been proposed for local resection of wide-based benign neoplasms unresectable by colonoscopy and of early stage malignant neoplasms with favorable prognostic factors. Nevertheless, transanal resection allows comfortable access only to the distal rectum, which explains in part the high rates of local recurrence.^{4,5} Transanal endoscopic microsurgery (TEM), proposed 25 years ago by Buess,^{6,7} can be considered a viable alternative in select cases because it combines the advantages of minimally-invasive local treatment with large full-thickness local resection and improved visualization. This study presents the results of a retrospective analysis of a large clinical series with up to 15 years of follow-up.

MATERIALS AND METHODS

This study is a retrospective analysis of a prospective database created in January 1993. Indications for TEM were benign rectal lesions judged unsuitable for endoscopic removal, early rectal cancer,

and invasive or metastatic rectal carcinoma treated with palliative intent. Inclusion criteria were depending on anatomic restrictions assessed by rigid rectoscopy to locate the lesion along the circumference and to measure its distance from the anal verge. Lesions were considered suitable for TEM treatment only when located within 12 cm of the anal verge on the anterior wall, 15 cm on the lateral walls, and 20 cm on the posterior wall, these being the limits of insertion of the peritoneum on the rectal wall.

The procedure was performed with original Richard Wolf (Knittlingen, Germany) TEM equipment, according to the standard technique described by Buess.^{6,7} In all cases, a full-thickness excision was made on the rectal wall to the perirectal fatty tissue, and the wound was closed with one or more running sutures secured with silver clips. All patients had a urinary catheter in place at the time of surgery, which was removed 72 hours after surgery in cases of anterior wall dissection, or 24 hours after surgery in all other cases. In cases of benign lesions, follow-up consisted of digital examination and rectoscopy every three months for the first year, then every six months. In cases of malignant lesions, tumor marker assays were performed every 3 months for the first year and every 12 months thereafter; additionally, full colonoscopy was performed at 12 months, and endoscopic ultrasound (EUS) and computed tomography (CT) were performed at 6, 12, and 24 months. Local recurrence was defined as any recurrence diagnosed more than six months after the TEM procedure and confirmed by biopsy.

We entered into the database information about patient characteristics, preoperative assessment, lesion location and histology, perioperative complications, and follow-up. Quantitative data are given as the mean, median, and range. Overall and disease-free survival rates were calculated using the Kaplan–Meier method. Patients with a minimum follow-up of 12 months were included in the analysis.

RESULTS

Between January 1993 and January 2007, 300 patients (185 males; mean age, 65.3 ± 11.6 (range, 25–94; median, 66) years) with rectal disease underwent TEM. The preoperative indications were 222 adenomas, 47 carcinomas, 4 rectal ulcers, 2 carcinoid tumors, 1 gastrointestinal stromal tumor (GIST), and 1 leiomyosarcoma. In addition, 5 adenomas and 18 carcinomas had previous attempts at endoscopic removal that resulted in unclear margins; these were referred for TEM for safe completion of the previous procedures. The distance between the lower edge of the neoplasm and the anal verge ranged between 2 and 20 (mean, 7.5 ± 2.5 ; median, 7) cm. Twenty-six uT2 and six uT3 lesions were treated by TEM for different reasons: 8 patients had benign histologies of biopsy samples on two occasions preoperatively, 13 were judged ineligible for abdominal resection due to their general condition, 5 refused the risk of temporary or definitive stomas, 3 received neoadjuvant radiotherapy and chemotherapy with apparent downstaging, and 3 had synchronous liver metastases and were treated with palliative intent.

Intraoperative Results

The mean operating time was 66.4 ± 42.8 (range, 15–240; median, 60) minutes. The intraoperative complication was inadvertent opening of the peritoneum in 13 (4.3%) cases. Ten patients were treated with direct suturing, and three required conversion to laparoscopic (two cases) or laparotomic (one case) anterior resection. The conversion rate was 1.0% (3/300). Intraoperative bleeding was always negligible; no intraoperative blood transfusion was required.

Postoperative Results

There was no 30-day mortality. The 30-day morbidity rate was 7.7% (23/300) (Table 1). None of the patients required a loop ileostomy. No urinary retention was observed. The mean length of hospital stay was 5.0 (range, 2–14) days.

Pathology Results and Staging

The mean surface area removed was 12.9 ± 9.5 (range, 2–56; median, 10) cm². Histological examination of the surgical specimens demonstrated an adenoma in 184 cases, a carcinoma in 90, carcinoid tumors in 2, leiomyosarcoma in 1, and GIST in 1. Four rectal ulcers were completely excised with no evidence of dysplasia. Of the 23 patients who underwent TEM with radical intent following incomplete endoscopic polypectomy without histologically-proven clear resection margins, 18 showed no residual disease and the remaining 5 had a diagnosis of adenoma. In the 43 patients with a preoperative diagnosis of adenoma, the definitive diagnosis was adenocarcinoma, with a discrepancy rate of 19.4% (43/222).

Postoperative staging of resected adenocarcinomas was as follows: 38 pT1, 37 pT2, and 15 pT3. Positive resection margins were detected in 9.8%, 2.6%, 16.2%, and 46.7% of patients with adenoma, pT1, pT2, and pT3 carcinoma, respectively. No specimen fragmentation occurred.

In all, 178 patients underwent preoperative EUS for staging (Table 2). EUS understaged 22 (12.3%) and overstaged 18 (10.1%) lesions. Of the 47 preoperatively diagnosed rectal cancers resected by TEM in the patients who had undergone EUS, 13 (27.6%) were understaged and 6 (12.7%) were overstaged. Specifically, in the 15 patients who had been referred to TEM for a suspected pT2 or pT3 carcinoma, an adenoma or a pT1 tumor was detected; in the 16 patients referred for TEM for a suspected adenoma or pT1 carcinoma, a pT2 or pT3 tumor was detected.

Oncologic Outcomes

Over a mean follow-up period of 82 ± 39 (range, 12–189; median, 100) months, 11 patients (6%) operated on for a rectal adenoma relapsed. Recurrence was observed in 6 of 18 patients with an adenoma, 1 of 6 with pT2, and 4 of 6 with pT3 tumors with positive resection margins. A second TEM procedure was performed in eight patients, laparoscopic anterior resection with coloanal anastomosis was performed in one patient, and abdominoperineal resection was performed in one patient. All were disease-free in further follow-up. One patient refused a second TEM procedure and was lost at follow-up.

Three patients underwent palliative TEM because of synchronous unresectable liver metastasis and were excluded from the follow-up analysis. No dropouts were observed among the cancer patients.

No recurrent disease was detected among the 38 patients with pT1 cancer at a mean follow-up of 60 ± 33 (range, 14–162; median, 51) months. Of the 49 patients with histologically-assessed pT2 and pT3 cancers, 8 (4 pT2 and 4 pT3) underwent immediate abdominal surgery, 22 (17 pT2 and 5 pT3) underwent chemoradiotherapy, and 19 (16 pT2 and 3 pT3) only received follow-up because they had either declined further surgery or adjuvant therapy or were deemed ineligible on account of age or co-morbidity. Local and/or distant recurrence was observed in 15 cases: 9 of 37 (24.3%) with pT2 cancer and 6 of 12 (50%) with pT3 cancer. Three of the eight patients who underwent salvage surgery, one with pT2 cancer and two with pT3 cancer, developed a local recurrence. Recurrence was diagnosed for these patients at 15, 6, and 29 months. All died of the disease (Table 3).

The overall 5-year survival rate of the cancer patients was 87.6%, and the disease-free rate was 82.2%. Stratified by tumor stage, the overall (Fig. 1) and disease-free (Fig. 2) survival rates were both 100% for pT1; 87.7% and 76.7%, respectively, for pT2; and 44.4% and 38.9%, respectively, for pT3 ($P < 0.001$). All of these estimated survival rates take into consideration not just the results of TEM, but also data from patients with additional treatments such as chemoradiotherapy and salvage surgery.

None of the patients with malignant neoplasms other than carcinoma showed recurrence at follow-up.

DISCUSSION

Abdominal surgery has long been considered the appropriate surgical treatment for rectal neoplasms. Nevertheless, anterior rectal resection and total mesorectal excision are burdened by high morbidity and mortality rates,² including urogenital dysfunctions.³ Transanal surgery with retractors, although less invasive, is associated with a consistent incidence of recurrence, especially for tumors of the upper and medium rectum.^{4,5,8,9}

Twenty-five years ago, the introduction of transanal endoscopic microsurgery (TEM) afforded the advantage of combining a less invasive transanal approach with low recurrence rates thanks to enhanced visualization of the surgical field which allowed more precise dissection. Initially proposed as a technique for excision of benign rectal neoplasms, TEM indications were extended to include “low risk” pT1 rectal adenocarcinomas¹⁰ with curative intent¹¹ and more invasive rectal adenocarcinomas with palliative intent. To date, only one randomized study¹² has compared the outcome after anterior resection (26 patients) with TEM (24 patients) for T1 rectal tumors. At a mean follow-up of 46 months, local recurrence (4%) and 5-year survival (96%) rates were similar in the two groups. These data suggest that TEM may offer some advantages over anterior resection for T1 tumors and achieve similar oncological results.

Patients who have T1 tumors with favorable pathologic features may undergo local excision alone with acceptable oncological outcomes,¹³ whereas those with unfavorable criteria will require radical surgery or adjuvant treatment.¹⁴ More recently, several authors^{15–18} have proposed that patients with pT2 tumors receive a combination of preoperative chemoradiotherapy and local resection by TEM with radical intent.

This retrospective analysis of a prospective consecutive series reports what may be the largest experience with TEM for excision of benign and malignant rectal tumors. Our analysis confirms that the procedure is safe and carries low postoperative mortality and morbidity rates. In line with previous studies that reported complication rates between 2% and 30%,^{11,19–22} only 23 of 300 patients (7.7%) experienced complications in our series, and no deaths occurred. The most common local complications, bleeding and dehiscence, were managed conservatively in the majority of cases. Also noteworthy was the occurrence in four patients of rectovaginal fistulas; therefore, special care should be taken when performing an anterior full-thickness resection in female patients. When a diagnosis of malignancy is not suspected at preoperative workup, a mucosectomy could be considered in case of anterior lesions.

The standard indication for TEM with curative intent is the treatment of adenomas and pT1 neoplasms of the rectum. With these indications, our recurrence rate was 11 of 222 (4.9%), which is comparable to that reported in smaller series. Other authors have compared TEM with transanal local excision according to Parks. Local excision was associated with a higher recurrence rate, ranging between 10% and 27%.^{21–24} The higher recurrence risk of conventional transanal surgery is most likely due to the lower rate of complete excision with tumor-free margins^{4,22,25–27} in conventionally-treated patients. These results derive from small retrospective studies and have not yet been confirmed by multicenter cohort studies.

Appropriate patient selection is key to obtaining satisfactory results with TEM. It is crucial to accurately evaluate the depth of tumor invasion and lymph node metastasis. So far, no recurrence has been observed among the 38 pT1 cancers confirmed at histology. EUS, with an overstaging risk of approximately 10%, appears to be the most accurate preoperative diagnostic tool for investigating tumor invasion of the wall.²⁸ This was also confirmed in our series, in which we noted a 12% risk of understaging and a 10% risk of overstaging among all lesions; the risks were 27% and 12%, respectively, when restricted only to detected cancers. Furthermore, 43 of 222 (19.3%) suspected adenomas, detected by tissue sampling and EUS, were found to be adenocarcinomas in the pathology examinations.

An important factor to consider in staging discrepancy in our series is the long period of recruitment: over the years, we have observed consistent improvement in EUS results. The limited reliability of preoperative diagnosis and staging resulted in a high number of pT2 and pT3

discovered in pathology examination. In those cases in which abdominal surgery was not contraindicated, patients were promptly referred for more radical treatments including anterior resection, total mesorectal excision, or even abdominoperineal resection. Of the eight patients who underwent immediate salvage surgery, three died of disease-related causes; this mortality rate is in line with that reported elsewhere. In all other cases unsuitable for abdominal surgery, the patients were either referred to adjuvant therapy (radiotherapy and chemotherapy) if not contraindicated, or just followed-up.

The role of TEM in the treatment of invasive carcinoma remains more controversial. Traditionally, local surgery has been used for palliation.²⁹ More recently, TEM in combination with neoadjuvant treatment has yielded promising results.³⁰ In our series, only three patients underwent neoadjuvant treatment for downstaging and downsizing uT2 cancers in order to become eligible for TEM with curative intent. Histology demonstrated that only one lesion was downstaged to pT1 cancer. Nevertheless, all three patients are presently free of disease. Further data will be needed to confirm this preliminary clinical experience.

In conclusion, TEM allows excision of benign rectal neoplasms with a low morbidity rate and has results comparable to those of conventional abdominal surgery. TEM also permits the curative treatment of malignant neoplasms that are histologically confirmed as pT1 carcinomas. In line with these observations, histologic diagnosis and preoperative staging are essential for an accurate selection of patients. We hold that such patients should be referred to specialized medical centers in which surgeons, endoscopists, gastroenterologists, and pathologists are experienced with TEM. When indicated, this innovative surgical technique can provide the potential benefit of a minimally invasive procedure, but without the risks associated with abdominal rectal surgery. Moreover, the analysis of this consecutive series of patients undergoing TEM suggests that the technique is safe and effective in the treatment of adenomas and pT1 carcinomas, with a recurrence rate comparable to that of conventional surgery.

REFERENCES

1. Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? *Gut* 2008;57:1690–7.
2. Morino M, Parini U, Giraudo G, et al. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. *Ann Surg* 2003;237:335–42.
3. Morino M, Parini U, Allaix ME, Monasterolo G, Brachet Contul R, Garrone C. Male sexual and urinary function after laparoscopic total mesorectal excision. *Surg Endosc* 2008 Oct 15. [Epub ahead of print]
4. Sakamoto GD, MacKeigan JM, Senagore AJ. Transanal excision of large, rectal villous adenomas. *Dis Colon Rectum* 1991;34:880–5.
5. Mellgren A, Sirivongs P, Rothenberger DA, Madoff RD, Garcia-Aguilar J. Is local excision adequate therapy for early rectal cancer? *Dis Colon Rectum* 2000;43:1064–74.
6. Buess G, Hutterer F, Theiss R, Bobel M, Isselhard W, Pichlmaier H. Das System für die transanale endoskopische Rektumoperation. *Chirurgie* 1984;55:677–80.
7. Buess G. Transanal Endoscopic Microsurgery (TEM). *J R Coll Surg Edinb* 1993;38:239–45.
8. Parks AG, Stuart AE. The management of villous tumours of the large bowel. *Br J Surg* 1973;60:688–95.
9. Nivatvongs S, Balcos EG, Schottler JL, Goldberg SM. Surgical management of large villous tumors of the rectum. *Dis Colon Rectum* 1973;16:508–14.
10. Hermanek P, Gall FP. Early (microinvasive) colorectal carcinoma. Pathology, diagnosis, surgical treatment. *Int J Colorectal Dis* 1986;1:79–84.
11. Mentges B, Buess G, Raestrup H, Manncke K, Becker HD. TEM results of the Tuebingen group. *Endosc Surg Allied Technol* 1994;2:247–50.
12. Winde G, Nottberg H, Keller R, Schmid KW, Bunte H. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. *Dis Colon Rectum* 1996;39:969–76.

13. Floyd ND, Saclarides TJ. Transanal endoscopic microsurgical resection of pT1 rectal tumors. *Dis Colon Rectum* 2006;49:164–8.
14. Bentrem DJ, Okabe S, Wong WD, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? *Ann Surg* 2005;242:472–7.
15. Lezoche E, Guerrieri M, Paganini AM, Feliciotti F. Long-term results of patients with pT2 rectal cancer treated with radiotherapy and transanal endoscopic microsurgical excision. *World J Surg* 2002;26:1170–4.
16. Borschitz T, Heintz A, Junginger T. Transanal endoscopic microsurgical excision of pT2 rectal cancer: results and possible indications. *Dis Colon Rectum* 2007;50:292–301.
17. Duek SD, Issa N, Hershko DD, Krausz MM. Outcome of transanal endoscopic microsurgery and adjuvant radiotherapy in patients with T2 rectal cancer. *Dis Colon Rectum* 2008;51:379–84.
18. Tjandra T. Long-term results in patients with T2–3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. *Tech Coloproctol* 2006;10:158.
19. Stipa F, Lucandri G, Ferri M, Casula G, Ziparo V. Local excision of rectal cancer with transanal endoscopic microsurgery (TEM). *Anticancer Res* 2004;24:1167–72.
20. Lezoche E, Guerrieri M, Paganini AM, Feliciotti F, Pietrantonio F. Is transanal endoscopic microsurgery (TEM) a valid treatment for rectal tumors? *Surg Endosc* 1996;10:736–41.
21. Heintz A, Morshel M, Junginger T. Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. *Surg Endosc* 1998;12:1145–8.
22. Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. *Dis Colon Rectum* 2005;48:270–84.
23. Lee W, Lee D, Choi S, Chun H. Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer. *Surg Endosc* 2003;17:1283–7.
24. Langer C, Liersch T, Süß M, et al. Surgical cure for early rectal carcinoma and large adenoma: Transanal endoscopic microsurgery (using ultrasound or electrocautery) compared to conventional local and radical resection. *Int J Colorectal Dis* 2003;18:222–9.
25. Sengupta S, Tjandra JJ. Local excision of rectal cancer: What is the evidence? *Dis Colon Rectum* 2001;44:1345–61.
26. Gavagan JA, Whiteford MH, Swanstrom LL. Full-thickness intraperitoneal excision by transanal endoscopic microsurgery does not increase short-term complications. *Am J Surg* 2004;187:630–4.
27. Steele RJ, Hershman MJ, Mortensen NJ, Armitage NC, Scholefield JH. Transanal endoscopic microsurgery: initial experience from three centres in the United Kingdom. *Br J Surg* 1996;83:207–10.
28. Smith N, Brown G. Preoperative staging of rectal cancer. *Acta Oncologica* 2008;47:20–31.
29. Bretagnol F, Merrie A, George B, Warren BF, Mortensen NJ. Local excision of rectal tumours by transanal endoscopic microsurgery. *Br J Surg* 2007;94:627–33.
30. Lezoche G, Baldarelli M, Guerrieri M, et al. A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. *Surg Endosc* 2008;22:352–8.

TABLE 1. Postoperative morbidity and treatment in 23 of 300 consecutive patients who underwent transanal endoscopic microsurgery

Type	Treatment
11 rectal bleeding	3 endoscopic hemostasis 3 transrectal packing 5 blood transfusion
5 suture dehiscence	3 medical therapy 1 TEM 1 abdominal surgery
4 rectovaginal fistula	2 transvaginal surgical suture 2 total parenteral nutrition
1 parietal abscess	antibiotic therapy
1 major incontinence	biofeedback therapy
1 rectovesical fistula	abdominal surgery

Table 1. Postoperative morbidity and treatment in 23 of 300 consecutive patients who underwent transanal endoscopic microsurgery

TABLE 2. Staging discrepancy between preoperative endoscopic ultrasound and histology

	<i>adenoma/pT1</i>	<i>pT2</i>	<i>pT3</i>	<i>Total</i>
u-T0/u-T1	130	13	3	146
u-T2	13 (1 post RT)	7 (2 post RT)	6	26
u-T3	2	3	1	6
Total	145	23	10	178

RT = radiotherapy.

Table 2. Staging discrepancy between preoperative endoscopic ultrasound and histology

TABLE 3. Oncological outcomes

	<i>Postoperative treatment</i>	<i>n</i>	<i>Recurrence (months)</i>	<i>Treatment</i>	<i>Follow-up</i>		
pT1	Postoperative RT-CT	3	0		all disease-free		
	Salvage surgery	0	0				
	No treatment	35	0				
pT2	Preoperative RT	5	0		all disease-free		
	Postoperative RT-CT	16	4 (12, 12, 10, 70)	1 AR, 3 none		1 disease-free, 3 dead	
	Salvage surgery	4	1 (15)	APR + CT			dead
	No treatment	12	4 (12, 12, 10, 13)	2 RT, 1 APR, 1 AR			3 disease-free, 1 dead
pT3	Postoperative RT-CT	5	2 (14, 13)	1 RT, 1 APR	1 dead, 1 disease-free		
	Salvage surgery	4	2 (6, 29)	2 CT		2 dead	
	No treatment	3	2 (12, 4)	none		2 dead	

RT = radiotherapy; CT = chemotherapy; AR = anterior resection; APR = abdominoperineal resection.

Table 3. Oncological outcomes

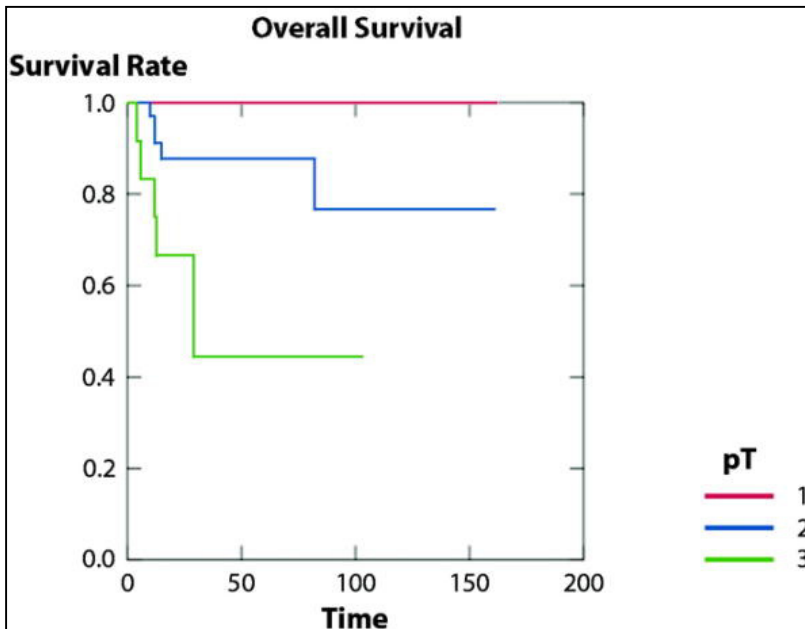


FIGURE 1. Overall survival rate of cancer patients stratified by tumor stage, including data of patients with additional treatments such as chemoradiotherapy and salvage surgery.

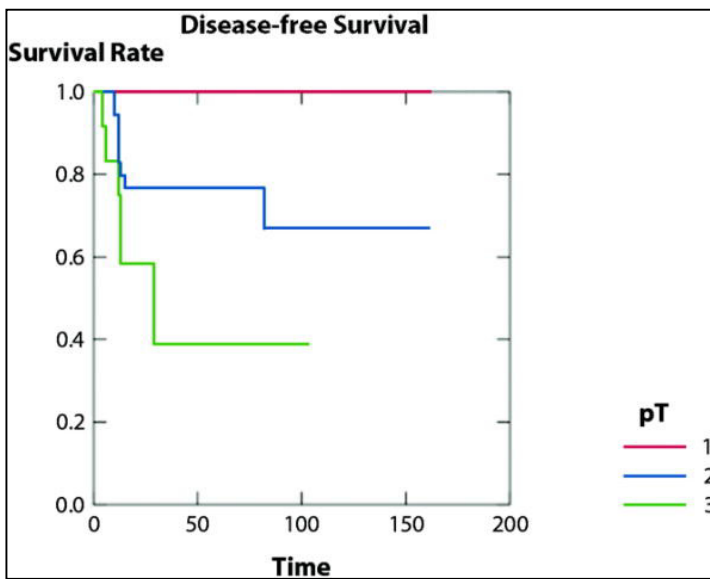


FIGURE 2. Disease-free survival rate of cancer patients stratified by tumor stage, including data of patients with additional treatments such as chemoradiotherapy and salvage surgery.