Review

Management of early rectal cancer

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Background: **Early rectal cancer (ERC) is adenocarcinoma that has invaded into, but not extended beyond, the submucosa of the rectum (that is a T1 tumour). Local excision is curative for low-risk ERCs but for high-risk cancers such management is controversial.**

Methods: **This review is based on published literature obtained by searching the PubMed and Cochrane databases, and the bibliographies of extracted articles.**

Results and conclusion: **ERC presents as a focus of malignancy within an adenoma, as a polyp, or as a small ulcerating adenocarcinoma. Preoperative staging relies on endorectal ultrasonography and magnetic resonance imaging. Pathological staging uses the Haggitt and Kikuchi classifications for adenocarcinoma in pedunculated and sessile polyps respectively. Lymph node metastases increase with the Kikuchi level, with a 1–3 per cent risk for submucosal layer (Sm) 1, 8 per cent for Sm2 and 23 per cent for Sm3 lesions. Low-risk ERCs may be treated endoscopically or by a transanal procedure. Transanal excision or transanal endoscopic microsurgery may be inadequate for high-risk ERCs and adjuvant chemoradiotherapy may be appropriate. There is a low rate of recurrence after local surgery for low-risk ERCs but this increases to up to 29 per cent for high-risk cancers.**

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Introduction

Early rectal cancer (ERC) is defined as invasive adenocarcinoma spreading into, but not beyond, the submucosa, that is a T1 tumour in the tumour node metastasis (TNM) classification[1–4]. These tumours have a smaller chance of metastasizing to local lymph nodes than adenocarcinoma invading deeper than the submucosa[2] owing to the paucity of lymphatics within colorectal mucosa. Neoplastic cells, confined to the colorectal mucosa, are correctly defined as dysplasia or adenoma in the UK. In the American and Japanese literature, the misnomers 'intramucosal carcinoma' and 'carcinoma *in situ*' are used. ERC may present as a polypoid carcinoma, a focus of malignancy within a large pedunculated or sessile adenoma, or as a small ulcerating adenocarcinoma[2].

ERC is a relatively uncommon finding in Western populations. The incidence of malignant colorectal polyps as a proportion of all adenomas removed varies between 2·6 and 9·7 per cent, with an average of 4·7 per cent[5]; 3–8·6 per cent of all resected colorectal adenocarcinomas are stage T1[4,6,7]. The incidence of ERC will rise following the start of the UK screening programme. In Japan, the incidence of T1 tumours removed by endoscopic polypectomy rose from 3·8 per cent in 1978 to 10·3 per cent in 1997[8].

The management of ERC aims to offer cure while minimizing the morbidity and mortality of the treatment. Anterior resection and abdominoperineal excision have a significant risk of death (30-day mortality rate less than 7 per cent), morbidity (35 per cent) and poor functional outcome[9]. They do, however, give the best chance of cure. Endoscopic or minimal access surgical procedures offer the opportunity of cure with less detriment. Adjuvant chemoradiotherapy may play a role. Staging of the ERC is critical to the management, with histological assessment the most important factor for predicting the risk of lymphatic spread. The term ERC will be used in the context of both a low and a high risk of lymph node metastases and local recurrence.

Methods

A literature search was conducted for the period from 1995 to 2006 using PubMed and Cochrane databases, and the search terms 'early rectal cancer', 'colorectal

polyp', 'colorectal cancer', 'polypectomy', 'endoscopic mucosal resection', 'local excision', 'transanal endoscopic microsurgery' and 'minimally invasive surgery'. The bibliographies of extracted articles were further cross-referenced.

Preoperative diagnosis and investigation

ERC may present with rectal bleeding or as an asymptomatic finding during screening. It may be difficult to identify during colonoscopy and clues, such as irregularity of the mucosa (mucosal pinkness, superficial granularity and nodularity, mucosal fading, depressions or haemorrhagic spots), should raise suspicion. Spraying of the abnormal mucosa with a soluble ink, such as indigo carmine dye, may render the lesion easier to visualize[1] by revealing the innominate or fine grooves that run circumferentially around the normal colonic mucosa[10]. These innominate grooves are lost over an ERC[11]. A further method of detection is air transformation in which depressed areas of mucosa are made more prominent by decreasing the air pressure within the colon; with maximal distension the lesion becomes flat[1]. Magnifying colonoscopy has further assisted the detection of ERC[12].

Endorectal ultrasonography is the most sensitive investigation for differentiating between T1 and T2 lesions, with an accuracy of 81–92 per cent[13,14]. It may also be used to assess residual tumour following polypectomy[15]. Pelvic magnetic resonance imaging (MRI) should also be performed to exclude extension of tumour from the submucosa into the muscularis propria[16]. One group has reported 94 per cent accuracy for T stage and 85 per cent for N stage[16]. Ultrasonography and MRI appear to be equally good at assessing lymph node involvement[14,17]. Lymph nodes over 8 mm in diameter in the shortest axis are usually malignant, although size may not be a reliable predictor of nodal involvement owing to the high frequency of enlarged, reactive lymph nodes adjacent to rectal cancers, and the ability of small lymph nodes to harbour metastases[18–20]. The recognition of new criteria, such as a spiculated or indistinct border and a mottled heterogeneous appearance, increases the ability to predict malignant lymph nodes accurately[17]. Computed tomography of the chest and abdomen may reveal lung or liver metastases. The rest of the colon must be screened for the presence of synchronous adenomas or carcinomas.

Future developments will focus on detecting lymph node metastases. There are a number of lymph node-specific contrast agents under investigation. Phase III trials have shown that the use of ultrasmall superparamagnetic iron oxide (USPIO) nanocolloid particles can help to differentiate metastatic from normal lymph nodes on MRI[21–23]. Second-generation USPIO particles have dendritic arms that can be labelled with antibody or fluorescent agents[24]. In the future, antibodies that are specific for colorectal cancer, such as the anticarcinoembryonic antigen antibody PR1A3, may be radiolabelled and used to detect metastatic lymph nodes[25].

Endorectal ultrasonographically guided needle biopsy of lymph nodes is feasible, but is not widely used[26,27]. Recent interest in transrectal ultrasonographically guided biopsy of possible local recurrence may reverse this[28]. Positron emission tomography (PET) is used routinely for investigating pelvic recurrence and has the potential to detect involved nodes, but the resolution for those of less than 1 cm is poor and their detection may be impossible owing to their close proximity to the primary tumour and the bladder[29,30].

There are a number of developing perioperative techniques for locating lymph node metastases. The theory of node mapping and sentinel lymph node (SLN) biopsy assumes that if the SLN is free of metastatic disease it is likely that all other regional lymph nodes will be clear[31]. A peritumoral injection of isosulphan blue is given and, within a few minutes, blue lymph nodes are easily visible among the yellow mesenteric fat[32]. Early results indicate that this method is good for predicting the nodal status of non-irradiated ERC[33]. In the future, this could theoretically be undertaken at the time of local excision of the ERC, perhaps through endorectal ultrasonographically guided needle biopsy. On the basis of SLN frozen-section histology, formal anterior resection would be performed if the node were positive.

Radioimmunoguided surgery was described in 1995, using ^{99m}Tc-labelled PR1A3, given 24 h before the operation[34,35]. The surgeon uses a sterile probe to examine the primary tumour, possible metastatic lymph nodes and any suspicious sites during surgery. This technique may find use after a primary ERC has been locally excised, with the probe being used to interrogate the mesorectal fat for 'hot' lymph nodes. Frozen-section examination of these nodes would then determine the nature of any further surgery.

Surgical options for early rectal cancer

Surgical options must encompass accurate histology, safe oncological surgical principles and the highest chance of cure. Any local treatment that destroys the tumour architecture or renders tumour tissue impossible to examine, such as electrocoagulation, endocavity radiation, and laser and cryotherapy, are not suitable for ERC. Snare polypectomy or endoscopic mucosal resection is used to treat polyps that are thought to be benign. Transanal excision or transanal endoscopic microsurgery (TEMS) is

necessary for larger tumours. The Kraske posterior trans-sacral proctotomy is occasionally used for the excision of ERC and large sessile adenomas[36,37]. Of historical note, the York Mason trans-sphincteric approach gave an excellent exposure of the rectum, but the complication rate was high[38].

The various options for the surgical treatment of ERC are described in *Table 1*. When the pathological staging is worse than expected before operation, it may be necessary for the patient to undergo further surgery. Patient choice, co-morbidity and body habitus will also affect this decision.

Polypectomy

Standard polypectomy

Routine polypectomy, using a snare, is undertaken during removal of adenomas that are found during flexible sigmoidoscopy or colonoscopy. It is suitable only for the pedunculated type of ERC, found incidentally after an adenoma has been removed.

Advanced polypectomy and endoscopic mucosal resection

These colonoscopic techniques are performed for sessile adenomas when a wide mucosal clearance of the polyp is required (*Fig. 1*). An accurate map of the adenoma is made before is treatment started. Once the adenoma has been delineated, usually with dye spraying, 1 in 10 000 epinephrine and saline is injected into the submucosa to elevate the adenoma. For advanced polypectomy, it is important that the lesion remains exactly at the summit of the artificial swelling[1], which is then snared and resected. A polyp that does not 'lift' on submucosal infiltration should be regarded as malignant. Endoscopic mucosal resection uses the strip biopsy method, as described by Karita and colleagues[39]. The lesion is marked with diathermy around its circumference and submucosal infiltration is performed. A barbed snare is used and the tumour removed in strips. Accurate histological examination is difficult and so this technique should be used only for tumours that are thought to be benign on preoperative staging. Mucosal tattooing just distal to the local excision site can prove invaluable at a later stage to identify the site if it is necessary to perform a further procedure.

Table 1 Possible options for surgical treatment of early rectal cancer

Surgical option	Pathological stage
Standard polypectomy	Pedunculated adenoma ERC pT1 Haggitt level 1–3
Advanced polypectomy or endoscopic mucosal resection	Flat and depressed adenomas < 3 cm ERC pT1 Sm1a and Sm1b without vessel invasion
Per anal excision or transanal endoscopic microsurgery	Large adenomas pT1 Sm1b and pT1 Sm2 pT1 Sm3 and possibly pT2 (in an unfit patient)
Anterior resection	pT1 Sm3 and possibly Sm2 Poor differentiation, vascular invasion, incomplete excision

ERC, early rectal cancer; pT, pathological tumour; Sm, submucosal layer.

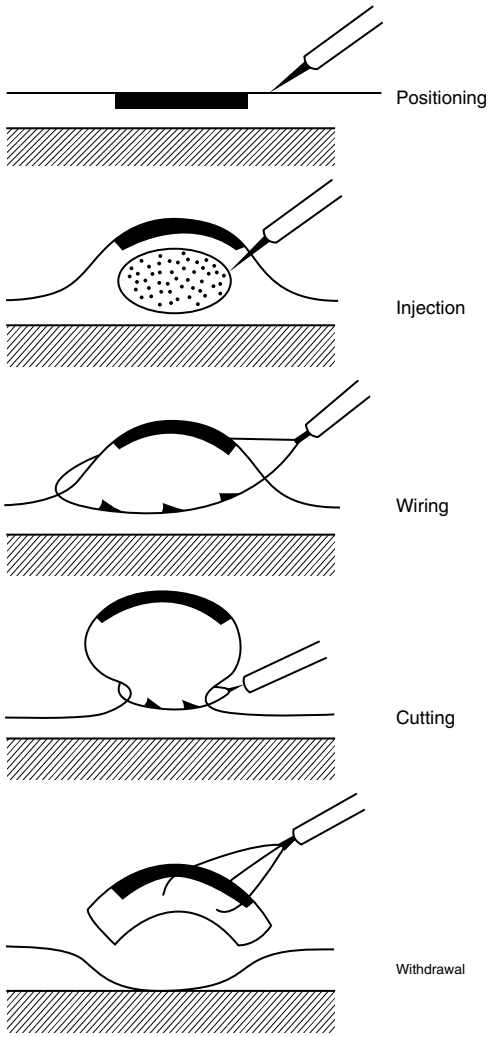

Fig. 1 Advanced polypectomy. Submucosal infiltration raises the polyp such that it can be removed by snare polypectomy with adequate clearance

Other methods of local excision

ERC may be removed either by Parks' per anal excision or by TEMS. The Trendelenburg lithotomy position is used for tumours lying posteriorly, the jack-knife position for anterior tumours, and the left or right lateral position, as appropriate, for lateral tumours.

Parks' per anal excision

Parks' per anal excision is possible for lesions within 6–10 cm of the anal margin[40]. The tumour is assessed under direct vision, with the aid of anal retractors. Headlight illumination or a fibreoptic light in the retractor may be used. A line of excision is marked with diathermy, allowing at least a 1-cm margin around the tumour. A full-thickness disc of rectal wall is removed with the tumour sitting in the middle of the disc. Although a full-thickness excision is possible on the anterior wall of the rectum, the vagina or prostate and seminal vesicles are close to the bowel wall and care must be taken not to damage these structures. For more proximally placed lesions, traction sutures or tissue forceps may be used to prolapse the tumour down into the distal rectum, but exposure can be difficult.

Once the disc of rectal wall has been removed, the underlying mesorectal fat can be palpated for enlarged lymph nodes, which may then be removed. The defect is usually closed using absorbable sutures. It is possible to leave the wound open if it is below the peritoneal reflection[41–43]. A technique has been described that uses an endoscopic linear stapler-cutter, which is placed at the base of the retracted tumour and then fired[44]. This does not, however, reliably excise the full thickness of the bowel wall.

Minimally invasive transanal surgery is a further modification and enables local excision of tumours lying above the peritoneal reflection[45]. A specially designed anal retractor is used, connected to an Octopus® (Medtronic, Minneapolis, Minnesota, USA) retractor holder. Endostaplers are used to perform full-thickness rectal wall excision and the anastomosis. Early results show that small tumours are easily removed with clear surgical margins and low morbidity[46]. The technique may also be accomplished for low tumours using the Salvati operating proctoscope[47].

Patients are able to eat normally immediately after surgery and generally leave hospital within 48 h. Morbidity is minimal, and typically confined to haemorrhage (less than 5 per cent) or urinary retention (less than 5 per cent)[48,49]. More important complications, such as rectovaginal fistula, may occasionally occur.

Transanal endoscopic microsurgery

TEMS was first described in 1984[50,51] and introduced to the UK in 1993. It uses a resectoscope to give a stereoscopic view of the rectum and distal sigmoid colon[52]. An exceptionally clear and magnified view of the mucosa allows precise handling of mucosal lesions. The procedure is associated with a low morbidity and mortality rate[53]. TEMS is theoretically suitable for tumours lying up to 25 cm (the furthermost margin of the tumour) from the anal verge[54]. It is more usual, however, to confine the procedure to tumours below the peritoneal reflection[49]. This is because of the risk of intraperitoneal perforation, inability to obtain preoperative staging with endorectal ultrasonography for tumours so proximally sited, and technical difficulty. It has been reported recently that full-thickness intraperitoneal excision of tumours does not increase short-term complications[55]. Lesions within 6 cm of the anal verge are best dealt with by Parks' technique as it can be difficult to maintain the carbon dioxide seal needed for TEMS in the anal canal[39,49].

A full-thickness rectal excision is undertaken when the tumour is extraperitoneal. For lesions in the intraperitoneal distal sigmoid and anterior upper third of rectum, a partial bowel wall excision is usually performed because of the danger of peritoneal perforation and so should be used only for benign lesions. Dissection in the submucosal plane is inappropriate for putative benign lesions because of the possibility of malignancy, and for malignant lesions because of the risk of an involved lateral excision margin. TEMS may be used to excise the base of a previous polypectomy site for further histological information. If malignancy is known before surgery, some have advocated the removal of mesorectal fat and continuing the dissection posteriorly until the presacral fascia is reached[54]. This is not generally advised, however, because a subsequent classical resection will encounter a spoiled mesorectal margin and technical difficulty. An excision margin of 1 cm is regarded as acceptable[56,57]. The rectal wall is closed with a continuous absorbable suture or secured by silver clips. It may be left open if it is below the peritoneal reflection[56].

Endoscopic posterior mesorectal resection has been described using dorsoposterior extraperitoneal pelviscopy and excision of the posterior mesorectum draining the lower third of the rectum[58]. This is achieved as a two-stage procedure in conjunction with TEMS for lower-third T1 rectal cancers. In a series of 11 patients undergoing this procedure, a median of 8 (range 4–20) lymph nodes was obtained; two patients had lymph node metastases and subsequently received adjuvant chemoradiotherapy. After a median of 48 (range 4–60) months, there was no evidence

of locoregional recurrence. One patient developed liver metastases 8 months after operation.

TEMS is technically challenging, the equipment expensive and the operating time may be prolonged. The operative morbidity rate is, however, low and similar to that encountered with transanal excision[56,59]. The use of wider-diameter resectoscopes may cause some minor manometric disturbance of the anal sphincter and this may be symptomatic. It usually resolves within a few weeks[60].

Classical surgery

Anterior resection is necessary for high-risk ERC, unless there are extenuating circumstances. It may be required for submucosal level (Sm) 3 and possibly Sm2 lesions, those with poor differentiation, lymphovascular invasion, a positive margin, or inadequate tissue for accurate histological assessment[61] (*Table 2*). Abdominoperineal excision for an ERC should be unusual as there are many sphincter-preserving techniques that can be employed[62].

Table 2 Histopathological features of low- and high-risk early rectal cancer

Low-risk early rectal cancer	High-risk early rectal cancer
Well or moderately differentiated adenocarcinoma and mucinous adenocarcinoma	Poorly differentiated adenocarcinoma and mucinous adenocarcinoma
	Signet ring and undifferentiated adenocarcinoma
No vascular or lymphatic invasion	Vascular or lymphatic invasion
Kikuchi Sm1 and possibly Sm2	Kikuchi Sm3 and possibly Sm2
Haggitt 1–3	Positive resection margin
	Relative factors
	Absence of lymphoid infiltration
	Tumour budding
	Poor demarcation at invasive front
	Poor differentiation at invasive front
	Cribriform-type structural atypia
	Position in distal third of rectum

Sm, submucosal layer.

Chemoradiotherapy

Complete response to chemoradiotherapy and its implications for early rectal cancer

There is mounting evidence of the benefit from adjuvant chemoradiotherapy in combination with local excision for some ERCs. A recent, somewhat controversial, study investigated the role of chemoradiotherapy in the non-operative treatment of rectal cancer. Habr-Gama and co-workers[63] treated 265 patients with resectable distal rectal cancer (mean 3·7 (range 1–7) cm from anal verge) with neoadjuvant chemoradiotherapy (5-fluorouracil, leucovorin and 50·4 Gy). Seventy-one patients (26·8 per cent) had a complete response (pretreatment clinical and radiological staging: 20 per cent T2, 69 per cent T3, 11 per cent T4). These patients had no further treatment. Twenty-two of the 194 patients (8·3 per cent of the whole cohort) who had an incomplete response to neoadjuvant chemoradiotherapy underwent surgery to remove the residual rectal ulcer (4 per cent T2, 87 per cent T3, 9 per cent T4; 41 per cent abdominoperineal excision, 59 per cent low or ultralow anterior resection) and were found to have no histologically detectable cancer (radiotherapy (y) pathological (p) T0 N0 M0). Mean follow-up was 57·3 months in the chemoradiotherapy-only group and 48 months in the operated group. There were three systemic recurrences in each group and two endorectal recurrences in the former group. Two patients died from their disease in the operated group. Five-year overall and disease-free survival rates were 88 and 83 per cent respectively in the operated group, and 100 and 92 per cent in the non-operated group[63]. This elegant study shows that chemoradiotherapy may, by itself, be curative in certain circumstances. These data also compare well with those of other studies which show that a pathological complete response to preoperative chemoradiotherapy is associated with improved local control and patient survival following classical resection and mesorectal excision[64].

Adjuvant chemoradiotherapy and local excision

It has been suggested that adjuvant chemoradiotherapy should be given when T2 rectal cancers have been excised locally[65], assuming that further surgery is not an option, as the risk of recurrence is unacceptably high. There is a less than 10 per cent chance of leaving malignant lymph nodes behind if the cancer is a well differentiated T2 lesion with no adverse features, but over 70 per cent risk if the cancer is poorly differentiated with lymphovascular invasion[66,67]. This has been found to equate to a 5-year local recurrence rate of 66 per cent for T2 tumours[65].

Recent data suggest that the local recurrence risk for ERC or T1 cancers, especially those with adverse prognostic features, is worse than first thought[68,69] and so it has been recommended that high-risk ERC should receive adjuvant chemoradiotherapy, assuming that further surgery is inappropriate[69–71]. The treatment typically consists of external beam radiotherapy using 53 Gy to the surgical bed, including 45 Gy over 25 fractions to the primary tumour site and pelvic lymph nodes, followed by a boost of 8 Gy over four fractions to the primary tumour site[65,68,70,71]. Chemotherapy based on 5-fluorouracil is given on weekdays during the radiotherapy course. In a retrospective study of neoadjuvant therapy, the 5-year local recurrence rate for T1 cancers was decreased from 11 to 0 per cent[65].

Preoperative neoadjuvant chemoradiotherapy may not only sterilize microscopic lymph node metastases but also reduce the likelihood of tumour cell implantation and subsequent recurrence at the local excision site[68]. However, its use for ERCs treated by local excision cannot be justified as many patients would be overtreated. Better preoperative staging with highly sensitive imaging techniques and molecular markers is necessary to define those high-risk ERCs that require neoadjuvant treatment.

Radiotherapy alone

Rectal adenocarcinoma is relatively resistant to radiotherapy. Treatment may be delivered as contact radiotherapy, delivering an increased dose to a small volume, or as interstitial brachytherapy used to give a boost of radiation into the cancer. External beam radiotherapy may supplement the dose to the deep part of the cancer and to the perirectal lymph nodes[72]. Contact therapy delivering an average of 95 Gy together with an interstitial brachytherapy boost of 24 Gy has resulted in a 5-year disease-free survival rate of 80 per cent and local control of 83 per cent for T1 rectal cancers[73]. T2 cancers fared far worse, with a 5-year disease free survival rate of 33 per cent and local control of 38 per cent. Improvement of local control for T1 cancers has been suggested to be dependent on the mobility of the tumour on digital palpation, the use of external beam radiotherapy and whether preradiotherapy transanal debulking of the tumour occurred[74].

Pathology of early rectal cancer

The management of ERC ultimately depends on the histological classification of the tumour and so it is important that specimens are handled correctly. Endoscopically excised polyps should be fixed in a volume of formalin that is at least five times greater than

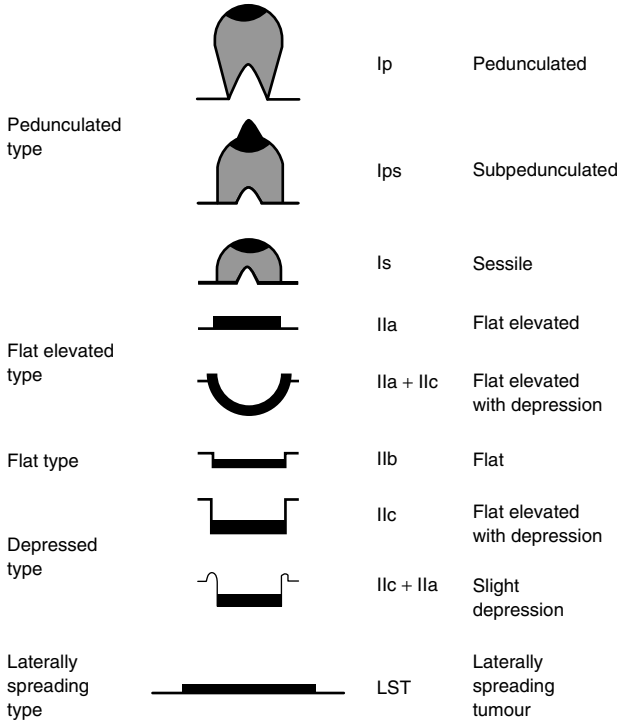

Fig. 2 Macroscopic classification of the morphology of early colorectal cancer according to Kudo[1]

that of the tissue. Local excision specimens are best delivered to the laboratory fresh. It is important that the pathologist knows the clinician's diagnosis, results of relevant investigations and the patient's previous treatment, especially radiotherapy or chemotherapy. Some authors advocate routine photography of the specimen[75], but an accurate description, together with a diagram, if necessary, may be satisfactory[76].

Polyps are processed whole when they are smaller than 1 cm, and sectioned to show the correct anatomical relationship between the polyp and the underlying tissues[77]. If the polyp is greater than 1 cm, its edges are trimmed to leave a central section containing the intact stalk[76]. The relationship between the head and the stalk is maintained and the stalk clearly identified. It should be noted that the polyp will usually have been placed under traction at the time of its removal and it is possible to create an elongated 'false' stalk. The tissue is fixed for 24 h to prevent fragmentation[78]. Occasionally the precise orientation of the polyp cannot be identified clearly; sectioning at several levels may then be needed to recognize the exact anatomical relationships. The entire lesion is submitted for histology.

Specimens retrieved after Parks' excision or by TEMS need to be pinned fresh to a cork board using dressmaker's pins around the entire circumference. This should be done

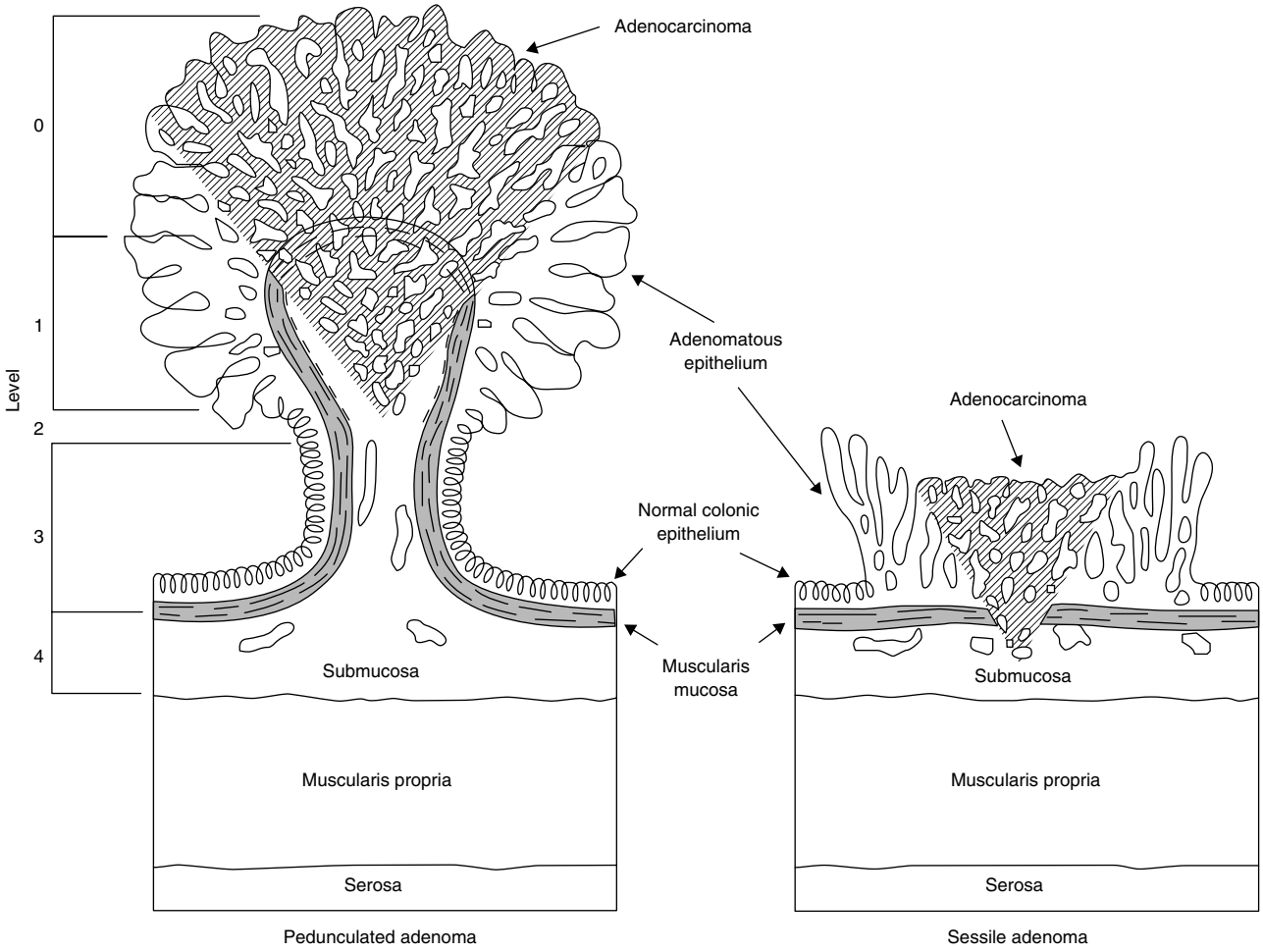

Fig. 3 Schematic view of submucosal invasion, after Haggitt and colleagues[81], from Haboubi and Scott[5]

soon after removal to avoid tissue shrinkage, which will render anatomical orientation and subsequent assessment of the resection margins difficult. The specimen is fixed for 24 h and then sectioned transversely into 3-mm slices, placed in sequentially labelled cassettes and submitted for histological examination.

Classification of early rectal cancer

A macroscopic classification of ERC has been proposed by Kudo and resembles that for gastric cancer (*Fig. 2*)[1]. Adenomas are subdivided into pedunculated or sessile, with approximately 42–85 per cent of early colorectal cancers being pedunculated and 15–58 per cent being sessile[79,80]. Adenocarcinomas in pedunculated polyps are less likely to have infiltrated the deep submucosal layer[79].

Dukes' staging of rectal carcinomas depends on having lymph node histology available and so has no application in local excision specimens. The TNM classification is now regarded as the most comprehensive system for staging rectal cancers[3]. ERC is necessarily a stage T1 tumour (a tumour invading the submucosa). It is the problem of predicting the N (node) score in T1 tumours that raises the management controversy.

Haggitt and colleagues[81] described submucosal invasion within a polyp (*Fig. 3*). This classification is widely used, although levels 1, 2 and 3 apply to pedunculated lesions only. An invasive carcinoma in a sessile polyp can only be a level 4 Haggitt lesion.

The Haggitt classification is less useful for sessile tumours. The Kikuchi classification aims at describing the depth of submucosal invasion into the submucosa and this is more readily applied to such lesions (*Fig. 4*)[79]. The Kikuchi classification divides the submucosa into thirds and within the uppermost third the horizontal spread of tumour has also been described separately. In a study of T1 sessile

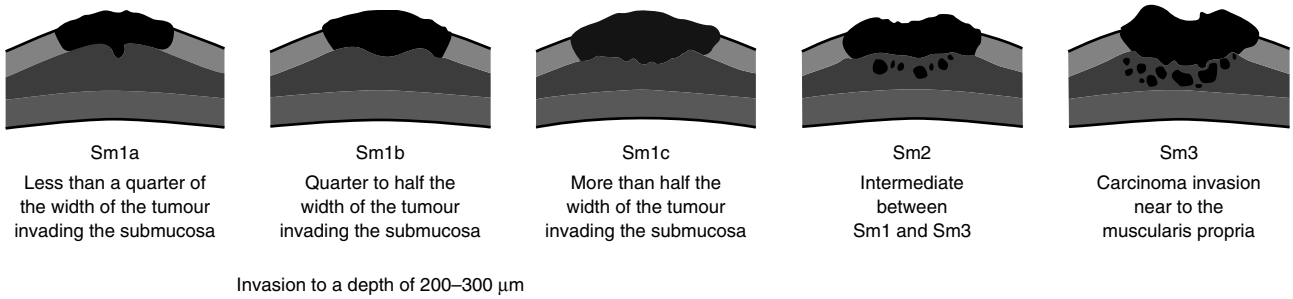

Fig. 4 Kikuchi classification of adenocarcinoma in a sessile polyp[79]. Sm, submucosal layer

adenocarcinomas, 35 per cent were Sm1, 45 per cent Sm2 and 20 per cent Sm3[79]. The Kikuchi classification can also be related to the Haggitt level; Haggitt levels 1, 2 and 3 are Sm1, and Haggitt level 4 can be Sm1, Sm2 or Sm3.

Risk factors for malignant invasion within an adenoma

Size is the most important factor in determining the risk of malignant transformation within a polyp. Over 5000 adenomas of less than 5 mm have been examined and none was found to be harbouring malignancy[82,83]; 38·5 per cent of adenomas larger than 1 cm had either high-grade dysplasia or carcinoma, and 78·9 per cent of those over 42 mm in size were malignant[82,83]. Villous adenomas have the highest risk of malignancy at 29·8 per cent, whereas tubular adenomas have the lowest at 3·9 per cent[83]. Tubulovillous adenomas have an intermediate risk of malignant transformation. Adenomas that are found in the rectum have the highest chance of malignant transformation at 23 per cent, compared with 6·4 per cent in the right colon and 8 per cent in the left colon[83].

Treatment selection for early rectal cancer

The choice of surgical treatment relies on patient, clinical, endoscopic, radiological and, crucially, histological parameters. Often the best plan is made retrospectively once the tumour has been removed and the histological stage confirmed[84]. Treatment by local excision alone requires consideration of the chance of subsequent development of local recurrence or involved lymph nodes being left behind. If the tumour is associated with a high risk of lymph node metastases and recurrence following local excision, early classical surgery (within 30 days) does not compromise the oncological outcome compared with primary classical surgery[85].

Treatment selection is based on the macroscopic classification of ERC according to Kudo[1], the substaging of T1 adenocarcinoma in pedunculated polyps according to Haggitt[81] and the substaging of T1 adenocarcinoma in sessile polyps according to Kikuchi[79]. This allows the ERC to be classed as having a high or low risk of recurrence. It is difficult to be prescriptive regarding the precise surgical treatment options. ERC in an elderly, frail patient will often be treated differently to a similar lesion in a young fit patient, and treatment will also depend on whether the ERC is high or low risk (*Table 1*).

Low-risk early rectal cancer

A low-risk ERC is defined as being a completely excised Haggitt level 1–3 or Kikuchi Sm1 T1 adenocarcinoma with no evidence of poorly differentiated adenocarcinoma or lymphatic or vascular invasion. It is debatable whether or not a Kikuchi Sm2 cancer should be considered as low risk; this would depend on whether other adverse features were present. It is now generally accepted that local excision, by either endoscopic polypectomy or transanal surgery, is adequate treatment for a low-risk ERC[5,9,57] (*Table 2*).

High-risk early rectal cancer

A high-risk ERC is commonly defined as one that has high histological grade, Sm3 and possibly Sm2 depth of invasion, together with the presence of lymphatic or vascular invasion (*Table 2*)[6,77,78,81,84,86–90]. The degree of lymphovascular invasion has been defined by the Japanese Society for Cancer of the Colon and Rectum[91]. Lymphatic (ly) or vascular (v) invasion may be absent (ly0, v0), slight (ly1, v1), moderate (ly2, v2) or massive (ly3, v3). Tumours with ulcerated or flat raised morphology are more likely to be high-risk ERCs than polypoid and sessile lesions[92]. Extension of the tumour to the resection margin automatically implies high risk.

The overall metastatic lymph node rate for ERC or T1 tumours ranges from 5·7 to 25 per cent[6,7,79,93–96]. The rate of lymph node metastasis increases with the Kikuchi

Table 3 Examples of positive node prediction using St Mark's Lymph Node Positivity Model

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	> 75	> 75	> 75	> 75	> 75
Depth of invasion	T1	T1	T1	T1	T1
Differentiation	Well	Moderate	Poor	Well	Poor
Histological type	Adenoca	Adenoca	Adenoca	Adenoca	Adenoca
Lymphocytic infiltration	Yes	Yes	Yes	No	No
Vascular invasion	No	No	No	Yes	Yes
Perineural invasion	No	No	No	Yes	Yes
Positive lymph node probability (%)	3·7	7·2	24	27·8	75·9

Adenoca, adenocarcinoma.

level: there is a 1–3 per cent risk with Sm1, 8 per cent with Sm2 and 23 per cent with Sm3[6]. These figures are similar to those in the original Kikuchi paper: 0, 10 and 25 per cent respectively[79]. Lymphovascular invasion is uncommon in T1 tumours and, when found, is associated with deeper submucosal invasion[6]. Polypectomy alone for high-risk lesions results in treatment failure, defined as recurrence and/or nodal metastasis, in 20–33 per cent of patients[88,89].

Further factors have been recognized that are related to the risk of lymph node metastases. Cribriform-type structural atypia and the absence of lymphoid infiltration imply a high risk of lymph node metastases[94]. The depth of submucosal invasion is related to lymph node metastases; none is found if the invasion is less than 1075 μm[96,97] and a cut-off for low risk of less than 1500 μm has been suggested[96]. For pedunculated polyps, the lymph node metastasis rate is zero if the cancer is confined to the head and neck or if the stalk invasion is less than 3000 μm, as long as there is no lymphatic invasion[97,98].

The location of early cancer in the rectum rather than elsewhere in the large bowel increases the chance of recurrence[79]. Furthermore, ERC lying in the lower third of the rectum carries a sixfold greater risk than lesions higher in the rectum[6,79]. Age has also been suggested by some as a risk factor, with 33 per cent of T1 tumours having positive lymph nodes in a group less than 45 years old, compared with 3·1 per cent in older patients[93]. Others, however, have not confirmed this[6].

The size of the ERC may or may not be implicated in the chance of nodal metastases[79,80,99]. Further factors indicating high risk include tiny clusters of undifferentiated cells found ahead of the invasive front ('tumour budding')[100,101], the cancer growth pattern at the submucosal invasive front, and tumour differentiation at the leading edge of the lesion[77,102,103]. These features have been investigated with respect to the relative risk of metastasis[104]. Five factors were examined: tumour budding, poor demarcation at the invasive submucosal front, poorly differentiated tumour in the invasive front, increasing depth and lymphatic invasion. Patients with fewer than four of these risk factors did not have nodal disease, whereas one-third of those with four and two-thirds with five had nodal metastases.

It is known that some T1 tumours behave very aggressively. Following abdominoperineal excision for T1/2 N0 cancers, a 5-year local recurrence rate of 12–14 per cent has been noted[105,106]. This suggests that individual cancer biology is a factor and, in the future, this may determine the initial surgical treatment and further adjuvant therapy for ERC. A number of molecular markers have already been investigated. Rectal cancers expressing the cyclin-dependent kinase inhibitor p27(kip1) have a significantly better prognosis than tumours that do not[107,108]. Sucrose–isomaltase expression is a predictor of colorectal cancer recurrence[109]. Altered expression of β-catenin and E-cadherin has recently been correlated with metastatic disease[110] and the DCC (deleted in colorectal cancer) protein seems to be a prognostic marker[111].

The St Mark's Lymph Node Positivity Model can be used to predict the probability of positive lymph nodes by inserting a number of variables into a web page pro forma (www.riskprediction.org.uk/index-lnp.php) A number of examples are given in *Table 3*. Unfortunately, it does not discriminate between the different Kikuchi levels of T1.

The greatest controversy relates to the definitive treatment of Kikuchi Sm2 tumours, which may be low or high risk depending on other histological factors. Recent advice in the Association of Coloproctology of Great Britain and Ireland's guidelines for local excision of rectal cancer is that further surgery should be considered if there is poor differentiation, vascular invasion, incomplete excision, or Haggitt 4 or Kikuchi Sm3 lesions[9]. This advice needs to be balanced against the risks of surgery for the individual patient.

Follow-up

After local excision, follow-up should include regular endoscopic surveillance of the rectum and of the scar in

particular. Careful follow-up to diagnose local recurrence early is necessary so that salvage surgery can be performed. Local recurrence may be extraluminal, presumably due to exfoliated cancer cells implanting into the raw area following local excision with subsequent healing of the overlying mucosa. Any follow-up protocol should include endorectal ultrasonography that allows imaging of the perirectal tissues[112,113]. Follow-up should continue long term, especially for those who have had radiotherapy as this delays the possible development of local recurrence[65,68,71]. In one study, the median time to local recurrence was increased from 13·5 to 55 months by radiotherapy[65]. A protocol similar to that followed for any other rectal cancer may be employed, although with more frequent assessment over a longer period[49,114]. Digital rectal examination and rigid sigmoidoscopy may be undertaken every 3 months for the first 3 years, every 6 months for the next 2 years and then annually[114]. Carcinoembryonic antigen and biochemical profile should be determined on each occasion. The use of endorectal ultrasonography, MRI and PET to detect local recurrence is advisable, although the appropriate frequency is the subject of debate. It has been suggested that endorectal ultrasonography should be performed at each follow-up appointment[114,115].

Prognosis

Disease recurrence after treatment of ERC depends on the histology and molecular biology of the cancer, lymph node involvement and type of surgery performed. Recurrence and survival rates are difficult to extrapolate from the published literature because of inconsistent definitions, the confusion of possible curative local excision for T1 and likely palliative local excision for T2/3 lesions, and the rarity of accurate histological staging. Overall, the recurrence rate is about 10 per cent for ERC treated by local excision[41,71,80,84,116,117]. The Oxford group has recently published the early results of TEMS for malignant tumours, which included 31 patients with ERC (four Sm1, 14 Sm2 and 13 Sm3)[117]. Three patients with a high-risk ERC underwent early salvage anterior resection (one Sm2 and two Sm3). At a median follow-up of 34 (range 1–102) months, three patients had developed local recurrence (one Sm1, one Sm2 and one Sm3). The overall 5-year disease-free survival rate was 79 per cent for ERC.

The US National Cancer Database has recently reported on 601 patients treated by local excision and 493 treated by standard resection for T1 rectal cancer. Patients with local excision had a lower 30-day morbidity rate (5·6 *versus* 14·6 per cent; $P < 0·001$) and a higher 5-year local recurrence rate (12·5 *versus* 6·9 per cent; $P < 0·003$); 5-year overall survival rates were similar (77·4 *versus* 81·7 per cent; $P = 0·09$). The 5-year overall survival was influenced by age and co-morbidities but not the type of surgery performed[118].

Very low rates of local recurrence and a 5-year survival rate approaching 100 per cent seem possible only if ERCs with favourable histology are included[65,71,84,119], although a local failure rate of 12–13 per cent at 10 years' follow-up has been reported[68,84]. For high-risk ERC, local recurrence can be as high as 29 per cent at 10 years[68,114]. Long-term follow-up beyond 10 years is necessary as local recurrence and cancer-specific deaths continue to occur[84,120]. It has been suggested that unresected disease in regional lymphatics is the cause of this local failure[68]. Long-term survival in this group may depend on adjuvant chemoradiotherapy but a 5-year cancer-free survival rate of approximately 74 per cent has been described[65,68,114]. Irrespective of the ERC itself, if there are lymph node metastases, the rate of disease recurrence is 36·4 per cent[80,103]. These data emphasize the importance of correctly predicting lymph node status and risk factors for recurrence, and the need for careful follow-up.

Treatment of recurrent disease

Recurrence from ERC treated by local excision may be confined within the mesorectal fascia rather than the pelvic side wall, as seen following classical surgery, and so salvage surgery may be technically less challenging[49]. Locally advanced disease, however, requiring the *en bloc* resection of adjacent pelvic organs, is frequently encountered[121]. Between 56 and 100 per cent of patients who do suffer a recurrence will be suitable for salvage surgery, usually of the classical type[49]. It is important to note that such salvage surgery may not afford the same outcomes as initial classical treatment[114,122]; disease-free survival rates of 20–53 per cent have been noted[65,68,114,121,123]. It has also been reported that there is decreased survival if resection is delayed rather than immediate at the time of clinical recurrence, if the local excision specimen has adverse pathological findings[124]. This again emphasizes the importance of the staging of ERC and the appropriate selection of treatment once the histology is known[122].

Overview

Early diagnosis and treatment of rectal cancer improves outcomes. The detection of an ERC ensures the best possible chance for the patient. In the future, ERC will be encountered more often with the deployment of mass screening programmes. Improved histological staging, relating this to the chance of lymphatic spread and lymph node metastases, should ensure that the correct surgical

procedure is performed. Classical surgery affords the best chance of cure, but for low-risk ERC local excision can match its outcomes while preserving rectal function. High-risk ERC can be treated by local excision, but oncological principles are compromised with correspondingly poor results.

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