Cancer National Specialist Advisory Group

Summary of evidence: management of early colorectal cancer

October 2013
Cancer NSAG summary of evidence: management of early colorectal cancer.

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1 Executive summary

Background
Early colorectal cancer, defined as pT1 (i.e. confined to the sub mucosa) has a good prognosis. With the advent of Bowel Cancer Screening in Wales (BSW) the incidence has risen. At present, there is a lack of high quality (level 1) evidence to guide management decisions in early colorectal cancer; this may be responsible for current variation in management.

Evidence
To inform this document the following have been included: an analysis of T1 lesions by the Welsh Bowel Cancer Audit (WBCA); published National, European and Japanese guidance; and a detailed literature search of prognostic factors including a meta-analysis. National Institute of Health and Clinical and Excellence (NICE) guidance was published in November 2011 but was unable to produce recommendations due to the lack of high order evidence. This document does not duplicate or supersede the advice published by NICE and is intended to act as a practical resource for MDTs.

Summary of recommendations for early colorectal cancer
Evidence grade is in brackets where this is appropriate (using methodology from Health Services Research unit, University of Aberdeen).

a. NICE recommend that early colorectal cancer specialist MDTs should be established and should discuss each case of early colorectal cancer. (C) see section

b. Each specialist and colorectal MDT should have agreed local protocols for the management of early colorectal cancer. (C) see section

c. Each MDT should have a method of estimating the risks of local recurrence and lymph node metastasis for each case of early colorectal cancer either developed locally or based on a method from the literature to advise patients on their further management. (B) see section

d. In each case, the perceived oncological risk should be balanced against locally determined risk adjusted post-operative mortality, and other patient related factors. (B) see section

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a Available at http://g-i-n.net
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e. Computer programs that determine individual patient’s risk for major surgery (for example CR-POSSUM) used by each colorectal MDT. (B) see section

f. The role of the pathologist is critical to establish a diagnosis of malignancy and provide sufficient assessment to allow risk stratification for recurrence. see section

g. Therefore:

i. The detailed pathology report should inform MDT discussion on further treatment and any need for a second opinion (B)

ii. For early colorectal cancer (CRC) or locally excised CRC there should be a pathology review of difficult cases by the regional expert panel and/or UK national panel. (C)

iii. The consistency of pathological assessment should be quality assured and satisfactory outcomes confirmed by audit.

iv. There should be accurate recording of this relevant data within Canisc.

v. There should be electronic reporting of these cases using CHIRP.

h. Rectal lesions with endoscopic features of potential malignancy should only be biopsied (not excised) and should be fully staged by endoscopic ultrasound and magnetic resonance imaging (MRI), prior to more formal treatment by local excision (endomucosal resection [EMR] or transanal endoscopic micro surgery [TEMS]) or by formal segmental resection. (C) see section

i. Where appropriate, patients with early colonic and rectal cancer should be considered for entry into randomised trials aimed at assessing the treatment of these conditions (e.g. Transanal Endoscopic Microsurgery and Radiotherapy in Early Rectal Cancer [TREC]). If not locally available, patients should be referred to centres participating in these trials. see section

j. The colorectal subgroup of the Cancer NSAG will work with partners to investigate developing a U.K or European collaborative database to collect data, assess current practice, establish outcomes and ensure consistent pathological reporting. Further research will ultimately define the optimum management of early colorectal cancer. see section
2 Background to, purpose of and use of this summary

A recent study of the surgical management of T1 cancers within Wales\textsuperscript{2} concluded that there is significant variance in approaches to management between MDTs. More detailed pathological data than is currently routinely collected within the all Wales clinical patient management system for cancer (Canisc) is needed to fully understand the differences. With increasing numbers of early cancers detected by the BSW programme, a lack of high quality evidence based guidance and differences in practice, a summary of evidence is urgently needed on an all Wales basis. NICE guidance was published in November 2011\textsuperscript{3} following a review of evidence and stakeholder consultation, but concluded that there was little high order evidence on stage 1 cancer and did not include specific guidance on early colorectal cancer (pT1). The Association of Coloproctology of Great Britain and Ireland (ACPGBI) has published a position statement on the management of polyp cancers\textsuperscript{4}. This document is not intended to duplicate or supersede the advice published by NICE/ACPGBI but to act as a practical resource for MDTs, and will be reviewed in light of subsequent publications.

The current evidence base for the optimal management of early cancer is weak. BSW and the Bowel Cancer Screening Programme in England (NHS BCSP) are prospectively collecting information as detailed in European guidelines\textsuperscript{5} using a dataset proforma. This will facilitate future analysis of T1 adenocarcinomas. In Wales, this collection of data will be facilitated by CHIRP which is a web-based reporting system linked to the Pathology Laboratory Information Management System (LIMS). This will include size, tumour grade (differentiation), depth of invasion, lymphovascular invasion and completeness of excision. The pathological analysis of a large national cohort of these early cancers will highlight features important in deciding between a conservative, non-operative approach or advising an oncological resection or other treatment.

This summary is intended to assist in decision making until more data on outcomes in early colorectal cancer are available. The evidence and references cited are only indicative. It should be used in conjunction with National and European guidance but informed by local assessment of the relevant literature. It is hoped that it will form a useful framework for discussion at MDTs. All involved in the management of early colorectal cancer should be conversant with the relevant literature and its limitations.
The following evidence has been used in compiling this statement for Wales:

a. National Guidelines from NICE, ACPGBI, Scottish Intercollegiate Guidelines Network (SIGN), British Society of Gastroenterology (BSG), Royal College of Pathologists (RCPPath), NHS BCS), and the Japanese Society for Cancer of the Colon and Rectum 2010.
b. European Guidelines.
c. A systematic literature review and meta-analysis of the risk of lymph node metastasis.
d. Analysis of T1 tumours 2009-2011 in Wales on behalf of the Cancer National Specialist Advisory Group (Cancer NSAG) and WBCA.
e. The ACPGBI and CR-POSSUM risk adjusted operative mortality models to predict individual risk

Grading of evidence and recommendations are according to the Health Services Research Unit, University of Aberdeen\(^b\). It must be recognised that there is little level 1 evidence currently available.

### 3 Introduction

This document focuses on the evidence available for MDTs to inform the management of early colorectal cancers or “polyp cancers”. If a lesion or polyp has been locally excised the debate is whether the patient should undergo radical surgery due to the risk of local recurrence and/or of lymph node metastasis (see below for more detailed discussion), or whether the risks of surgery, including morbidity, outweigh the risk of recurrence based on the histopathology report. The evidence should be presented to the patient and a decision made on an individual basis, balancing these potential risks.

NICE has recently published “Guidelines for the management of colorectal cancer”\(^3\) which includes the management of stage 1 (pT1/2N0) colorectal cancer (section 3.2). NICE did not specifically address early colorectal cancer (pT1) due to the lack of high order evidence necessary to formulate guidelines. The guidelines do highlight the importance of addressing the issue of early disease as it is being detected more commonly and reiterate their 2004\(^6\) advice that early colorectal cancer MDTs be established.

\(^b\) Available at http://g-i-n.net
Both colon and rectal cancers have been considered, and the evidence regarding both have been presented together because of the similarities in diagnosis, morphological appearance and histology. There are some differences in treatment, and where appropriate these have been presented separately.

4 Definition of early cancer

Historically, early colorectal cancer was regarded as Dukes’ A (T1/T2N0 or Stage 1) having a 5-year cancer specific survival of 95% following R0 resection\(^7\).

In 2007 the RCPath defined early colorectal cancer as “invasion into the sub-mucosa”. Therefore for the purposes of this summary early colorectal cancer is defined as pT1 as stated in the RCPath “Data set for Colorectal Cancer 2\(^{nd}\) edition 2007”\(^8\) and BSCP “Reporting lesions in the NHS BCSP” 2007\(^9\).

Carcinoma “in situ” (invasion of the lamina propria) is not recognised as malignant in the UK (in contrast to Japan\(^10\)) but is classified as high-grade dysplasia\(^11\). Therefore interpretation of the Japanese literature requires caution.

Nodal status can be confirmed after segmental resection but cannot reliably be determined beforehand by current imaging techniques. T1/T2 lesions can be identified following pathological assessment after local excision but for accurate T staging the specimen needs to be full thickness or at least contain muscle.

In the absence of reliable imaging for the determination of lymph node involvement\(^3\) a number of observational studies have identified prognostic pathological factors for the risk of loco regional recurrence. The evidence base on which to apply these in any individual T1 case is, however, weak. These factors include resection margins, depth of invasion, lympho-vascular invasion and tumour budding. These have been refined by classifications of polyp morphology largely based on the level of invasion\(^12, 13, 14, 15, 16, 17, 18\).
5 Pathology overview

Accurate pathological assessment is pivotal in the management of early colorectal cancer.

5.1 Invasion

A difficult area of assessment in the diagnosis of early colorectal cancer is whether actual invasion is present or whether there is only epithelial misplacement (pseudo invasion). Many prolapsed polyps, particularly in the sigmoid colon, show epithelial misplacement and in the presence of ulceration and inflammation it can be difficult to differentiate this from invasive adenocarcinoma.\(^{19}\)

5.2 High-grade dysplasia

The features of high grade dysplasia together with the diagnostic pitfalls are described in detail in “Reporting lesions in the NHS bowel cancer screening programme”\(^{9,19}\). In particular it is worth noting that high-grade dysplasia can be over diagnosed from biopsies.

A report of high-grade dysplasia should be taken in the context of the endoscopic appearances. The presence of high-grade dysplasia in a biopsy should raise the suspicion of a co-existing focus of cancer and lead to “en bloc” resection of the polyp. To enable subsequent identification of polyps that may need further excision the BSG and BSW guidelines advise that all polyps greater than 1 cm should be marked by tattooing at the time of endoscopic resection or biopsy.

To prevent over treatment of these benign adenomas BSW and the NHS BCSP are proposing the double reporting of all early colorectal cancers and that all slides from pT1 cancers are collected and digitally scanned for assessment and reproducibility of diagnostic risk factors.

5.3 Prediction of recurrence and/or nodal involvement

The prediction of recurrence, after local excision or polypectomy, is central to patient management.\(^{12,20,21}\).

Whilst the aetiology of local recurrence is debated, particularly in the rectum, the following definitions are used here:\(^{22}\)

a. **Intraluminal**: recurrence in the mucosa or bowel wall.
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b. **Nodal**: recurrence in the regional lymph nodes.

c. **Loco regional**: this embraces both intraluminal and loco regional as in the case of the rectum it may be difficult to determine the origin if the recurrence involves the bowel and regional nodes.

d. **Distant**: outside that segment of bowel and lymph node drainage e.g. liver, lung, para aortic nodes.

The factors that may influence the risk of recurrence are discussed below.

Excepting margin involvement, which predicts intraluminal recurrence, most systems use histopathological factors to try to predict the risk of nodal involvement and therefore locoregional recurrence. A number of systems have been described which estimate this risk but their reliability is compromised by incomplete/piecemeal excision and therefore is subject to inconsistent reproducibility between pathologists. There is also debate about the definitions in reporting these variables and most studies are retrospective. Direct observations can be made from studies of radical resections but cohort numbers in publications are usually low. Studies following local resection require longer follow up to be assured of their reliability.

### 5.3.1 Tumour morphology

A polyp cancer with an area of either irregularly folded, distorted, small tubules or the lack of any tubular formation should be classed as poorly differentiated. Marked cytological pleomorphism is usually seen in these poorly differentiated adenocarcinomas. Ulcerated or depressed polyps should be reported as non-polypoid. These lesions have an increased risk of lymph node metastasis and of local recurrence\(^{23}\).

### 5.3.2 Margin involvement

Peripheral and deep margin involvement by adenocarcinoma should be recorded. Margins are currently described as involved if the clearance is <1mm (current RCPath recommendation\(^8\)). Some authors prefer 2mm or even 5mm, which emphasises the confusion surrounding this topic in the literature, but further collaborative studies will clarify. Allowance can be made for cauterised tissue.

Further surgery, whether local excision or oncological resection, is recommended for margin involvement because of the high risk of local recurrence\(^3\). Determining this in polypectomy
specimens from endoscopic treatments can prove difficult. Whilst the pathology report may suggest an involved margin the depth of tissue destruction beyond this created at the time of polypectomy may, in reality, be more. The clinical margin of clearance may therefore be greater than that reported by the pathologist. Endoscopy reports should be specific as to the method of polypectomy performed and a statement should be made by the endoscopist about their assessment of complete or incomplete excision of any resected polyp. Comments should also be included in the report as to whether any further treatment was given to the polyp base (such as argon plasma coagulation).

5.3.3 Depth of invasion

There are many methods for measuring the depth of invasion into the submucosa that can sub-stage pT1 lesions and each has its advantages and disadvantages.

The Haggitt system defines the level of invasion according to the following criteria (see figure 1):

- Level 1 - carcinoma invading through the muscularis mucosae into the submucosa but limited to the head of the polyp.
- Level 2 - carcinoma invading to the level of the neck of the adenoma.
- Level 3 – carcinoma invading any part of the stalk.
- Level 4 – carcinoma invading into the submucosa but above the muscularis propria.

This system applies only to pedunculated polyps as sessile polyps were considered as level 4 lesions due to involvement of the submucosa. Haggitt concluded that only in level 4 lesions was there a significant risk of nodal involvement (27%). Although level 3 had no involved nodes some developed recurrence. This emphasises the need to take all factors into account. Matsuda et al reported a large series of pedunculated polyps (n=384) using Haggitt lines and came to the same conclusion, putting the risk for level 3 & 4 at 6%. 
The Kikuchi classification was developed for both sessile and pedunculated polyps and is defined as:

- **sm1** – slight submucosal invasion from the muscularis mucosa to the depth of 200 - 300 µm
- **sm2** – intermediate invasion
- **sm3** – carcinoma near the inner surface of the muscularis propria

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**Figure 1** Haggitt classification (reproduced from Haggitt et al 1985 with kind permission from Elsevier®).

**Figure 2** Kikuchi classification
(By permission of Mayo Foundation for Medical Education and Research. All rights reserved).

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This article was published in Gastroenterology, 89, Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD, Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy, 328–336. Copyright Elsevier 1985.
This is now more commonly interpreted as described by Kudo 1993\textsuperscript{26}.

sm1: superficial third,
sm2: middle third
sm3: deep third

Using the Kikuchi/Kudo definition, lymph node metastasis rates have been variably identified as shown in Table 1.

**Table 1 Published lymph node metastasis rates using the Kikuchi definitions**

<table>
<thead>
<tr>
<th></th>
<th>sm1</th>
<th>sm2</th>
<th>sm3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Son (2008)\textsuperscript{27}</td>
<td>3.1%</td>
<td>14.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Wang (2005)\textsuperscript{28}</td>
<td>2.8%</td>
<td>7.0%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Nascimbeni (2002)\textsuperscript{22}</td>
<td>3%</td>
<td>8%</td>
<td>23%</td>
</tr>
</tbody>
</table>

The disadvantage of using the Kikuchi definition in endoscopically resected polyps is that the specimen does not usually include the muscularis propria and so this classification system is unreliable.

The absolute depth of invasion has been proposed as a more accurate method of assessing invasion\textsuperscript{17, 29}. Indeed it has been suggested that a submucosal invasion depth of 1mm for sessile and 3mm for pedunculated tumours is significantly associated with an increased risk of lymph node metastasis\textsuperscript{29}.

In approximate terms the above findings translate into a risk of lymph node of involvement shown in table 2.
Table 2 Comparison of percentage risk of lymph node metastasis using three different systems

<table>
<thead>
<tr>
<th>System</th>
<th>Category</th>
<th>% Risk of lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedunculated Pedunculated</td>
<td>Levels 1,2</td>
<td>0</td>
</tr>
<tr>
<td>Haggitt (from Matsuda 2011)</td>
<td>Level 3,4</td>
<td>6</td>
</tr>
<tr>
<td>Sessile Sessile</td>
<td>Sm1</td>
<td>3</td>
</tr>
<tr>
<td>Sessile Kikukchi</td>
<td>Sm2</td>
<td>8</td>
</tr>
<tr>
<td>Sessile Kikukchi</td>
<td>Sm3</td>
<td>23</td>
</tr>
<tr>
<td>Depth of Invasion Uneo</td>
<td>Width &lt; 4 mm</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Width &gt; 4 mm</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Depth &lt; 2 mm</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Depth &gt; 2 mm</td>
<td>17.1</td>
</tr>
</tbody>
</table>

5.3.4 Lymphovascular invasion

Lymphovascular invasion is defined as definite invasion of endothelial-lined spaces in the submucosa. If present, there is a significant risk for lymph node metastasis. This variable is often regarded as the most important prognostic factor.23

Although often reported collectively as “lymphovascular invasion” the differing components have separate significance and are important to identify. Immunostaining with LEM D 2–40 (for lymphatics) and CD34 (for capillaries/veins) will help with the diagnosis of lymphovascular invasion and aid in differentiating the type of vessel involved.30

The risk can be summarised as;

a) Lymphovascular invasion absent 11% risk of nodal metastasis
   Lymphovascular invasion present 32% risk of nodal metastasis22

b) Lymphatic invasion absent 1% risk of nodal metastasis
   Lymphatic invasion present 25% risk of nodal metastasis31

c) Venous permeation absent 7% risk of nodal metastasis
   Venous permeation present 31% risk of nodal metastasis31
5.3.5 Tumour budding

Small islands or single cell infiltration of cancer cells at the front of tumour invasion constitute tumour budding. This has been identified as an unfavourable risk factor (15.5% risk of lymph node metastasis)\textsuperscript{23, 31}, but there are problems with reproducibility and consistency of definition\textsuperscript{17, 32}. The most commonly accepted definition is provided by Morodomi\textsuperscript{32} whereby budding is defined as either isolated undifferentiated cancer cells or clusters of five or six cancer cells forming a microtubular structure, which appeared to bud from large cancerous glands.

Adoption of this definition would allow evaluation of the value of budding as a prognostic indicator.

5.3.6 Location

Screen detected early colorectal cancer tends to be more distal and a significant number are low in the rectum\textsuperscript{14}. This has implications for further treatment, particularly surgery. There is debate as to whether location of tumour has any impact on the risk of lymph node metastasis, however data is inconclusive\textsuperscript{33, 22}.

5.3.7 Size

Ever since Morson’s original paper\textsuperscript{34} there has been debate as to importance of lesion size. Bach et al (2009)\textsuperscript{35} in a prospective study of TEMS resections concluded that lesions larger than 3cm are at high risk of loco regional recurrence. An objective measure of depth and width of the adenocarcinoma has been recommended by Ueno (2004)\textsuperscript{17}.

5.3.8 Molecular markers

In the future molecular markers may improve selection criteria for subsequent management. Where appropriate, informed consent from the patient should be sought and samples submitted for research.
6 Assessment of the risk of recurrence in individuals

The purpose of pathological assessment is to determine which patients are at “high risk” of locoregional recurrence and thus require further treatment, mainly surgery, based on the risk factors considered above set against the risk of surgery. Such lesions would include those with:

- a. cancer within 1mm of the resection margin
- b. poor differentiation
- c. lymphovascular invasion
- d. Sm3 and Haggitt 4

Conversely other lesions (low risk), have a risk of recurrence that is probably below the risk of intervention e.g. SM1, Haggitt 1, 2, or 3.

There are factors to be taken into account determining an individual’s risk other than Kikuchi and Haggitt levels. These are outlined in appendix 2 and 3.

As most series have low power, larger data bases are required. Attempts have been made to use computer models for accurate prediction and clarification.

Attention is drawn to the papers by Mainprize and Tytherleigh that discuss this in relation to the rectum.

7 Risk adjusted mortality: balancing the risk of recurrence against operative mortality

The risk of recurrence following local excision needs to be weighed against potential operative morbidity and mortality.

A recent audit of Welsh patients treated by surgical resection with T1N0 disease, between April 2009 and March 2011, found a 30 day mortality rate of 3%. This data highlights that oncological resection is not without considerable risk. This mortality data is for “all comers” and it must be remembered that in any individual the risk of post-operative death is not uniform.
Individual mortality risk is dependent on several variables relating to the patient and their co-morbidities. There are two readily available risk adjustment models\(^3\) that attempt to predict an individual patient’s mortality risk, having adjusted for other risk factors. These are the ACPGBI Mortality Model\(^3, 37\), which is specific to colorectal cancer patients, and the CR-POSSUM\(^3, 5, 37\) model which is applicable to all colorectal surgical procedures. Table 3 summarizes the variables used in each model.

**Table 3 Components of the ACPGBI and CR-POSSUM models.**

<table>
<thead>
<tr>
<th>ACPGBI Model(^38)</th>
<th>CR - POSSUM(^37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Cancer Resection Status</td>
<td>Cardiac Failure</td>
</tr>
<tr>
<td>ASA</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Cancer stage (Dukes’)</td>
<td>Pulse</td>
</tr>
<tr>
<td>Operative Urgency</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
</tr>
<tr>
<td></td>
<td>Operation Type</td>
</tr>
<tr>
<td></td>
<td>Peritoneal Contamination</td>
</tr>
<tr>
<td></td>
<td>Malignancy Status</td>
</tr>
<tr>
<td></td>
<td>CEPOD classification</td>
</tr>
</tbody>
</table>

Of the two models, the ACPGBI model is the simpler to use. However, it is a model that was developed on symptomatic bowel cancer patients undergoing both elective and emergency surgery\(^38\). In the context of a younger, fit patient with early stage disease the ACPGBI model is unlikely to usefully discriminate risk as accurately between patients, as the only variable in the model that will then differ between patients will be the ASA status. The CR-POSSUM model is more complex but was developed on both benign and malignant colorectal diseases treated with minor, intermediate and major surgery\(^37\). Neither model has been specifically developed for patients with early stage malignant disease.

If CR-POSSUM is to be used to aid decision making at the MDT meeting due to its complexity, the score and consequential risk should be calculated prior to the meeting. This can easily be achieved using on-line risk prediction software\(^3\) available at [http://www.riskprediction.org.uk](http://www.riskprediction.org.uk)

Cardio-pulmonary exercise (CPEX) testing is gaining acceptance as an individual risk model. It has the advantage of giving a true physiological assessment of risk for each individual for
major surgery. However, for various reasons, certain patients may not be able to undertake or complete the test so it cannot be used in every patient.

8 Pre-treatment staging

8.1 Endoscopy

Polyp assessment by the endoscopist can identify lesions at high risk of containing early cancer and sub mucosal invasion before any endoscopic treatment is undertaken. Accurately identifying such lesions will allow the initial endoscopist to determine if an immediate attempt at polypectomy should be performed or if it is best to take simple biopsies followed by further staging investigations and a complex polypectomy at a later date with adequate informed consent from the patient. If local expertise is not available, referral should be made to a specialist in complex endoscopic polypectomy techniques.

Assessment of the polyp includes:

- using the Paris classification\(^{18}\), of pit pattern recognition and granularity etc;
- combinations of techniques such as high definition endoscopy, narrow band imaging and dye spraying;
- inspection of macroscopic appearances such as a flat or hard lesion with depression, ulceration, (Paris 0-11a+c), non-granular, advanced pit pattern or failure to lift on sub mucosal injection are suspicious features of invasive disease;
- polyp size is more controversial. If sub mucosal invasion is present and there is a low risk of recurrence (not sm3) then en-bloc resection (by EMR or TEMS for rectal lesions) may be curative and gives the pathologist the best chance to assess the resection margins and other risk factors more accurately than simple polypectomy\(^{39}\).

For rectal lesions there are important differences in treatment options available and in the consequences of radical treatment. Because of this, rectal lesions should be accurately staged radiologically prior to any formal attempt at polypectomy as doing so may affect the findings of these important staging investigations and lead to a less than optimal treatment strategy for the patient.
8.2 Imaging

In the context of early colorectal cancer the important considerations are: 3, 40, 41, 42.

a. exclusion of distant metastasis;

b. assessment of N stage;

c. determination of T stage (particularly in the rectum if N and M staging are negative).

CT scanning of the chest, abdomen and pelvis should be performed to determine if there is metastatic disease. These findings may well change the treatment strategy from that of a radical approach to one aimed at achieving acceptable local symptom control whilst allowing the patient to commence treatment for systemic disease more quickly.

For rectal lesions, digital examination cannot be relied on for staging3. For early rectal lesions an MRI and/or endoscopic ultrasound (EUS) should be performed. This will assist in clarifying T stage and local nodal status. It is not uncommon to find a discrepancy between imaging, endoscopic and ultimate path staging. If the lesion is invasive, MRI allows assessment of the likelihood of a R0 resection with clear circumferential margins. EUS is the most accurate modality for the determination of rectal T stage and it should be performed if local excision is contemplated3. Therefore in endoscopically suspicious early rectal lesions, EUS should be performed prior to any formal polypectomy as the latter may distort the subtle anatomy of the layers in the rectal wall making interpretation of EUS inaccurate. If an attempt at complete removal by polypectomy has been previously performed, identification of the polyp site may not be possible rendering EUS assessment unreliable.

Over staging a benign rectal polyp or an early rectal cancer as a more advanced lesion may preclude acceptable local excision and lead to unnecessary radical rectal resection or chemoradiotherapy with its significant morbidity. It may also increase the potential risk of permanent stoma formation and deleterious effects on quality of life. If EUS is unavailable, MRI/ endocoil can also be used.

The following should be noted:

a. there is no reliable imaging modality to determine N stage. Accuracy of the available imaging modalities range from 56-75%3;

b. there are particular problems with imaging low in the rectum in assessing local spread3;
c. a PET scan may be positive in the presence of a benign polyp\textsuperscript{43};
d. in the future endoscopic ultrasound of the colon may be employed to
determine the local T stage for colonic cancer.

9 Treatment options after local excision, including endoscopic resection

Treatment options include:

a. intensive clinical follow-up;
b. further local excision;
c. further local excision and/or radiotherapy/chemo-radiotherapy (awaiting
further evaluation in trials such as TREC);
d. oncological resection.

T1 lesions can be stratified as low or high risk to inform this choice. Completely removed
low risk lesions do not require further treatment other than follow up. The timing should be
established locally but may include such measures as early endoscopic inspection of the
polypectomy site (e.g. at 3 months).

There is a very limited place for re-excision of incompletely excised lesions, even for low risk
lesions as there is an increased risk of local recurrence particularly low in the rectum\textsuperscript{20, 49}.

9.1 Surgery

Surgeons managing early colorectal cancer should be fully cognisant of the relevant
literature\textsuperscript{22}. They should be able to offer laparoscopic surgery to suitable patients, have
sufficient volume of work in this area, be able to present audited outcomes and follow
national guidelines for the management of colorectal cancer\textsuperscript{44}. They should have developed
networks for accessing treatment of suitable cases by ESD and TEMS.

Patients should be offered laparoscopic or laparoscopically assisted resection if suitable with
early colorectal cancer where formal resection is advised or chosen by the patient\textsuperscript{45, 46}.
Centres offering laparoscopic resection should have sufficient volume of work in this area, be able to present audited outcomes and follow national guidelines for the management of colorectal cancer.

The need for oncological resection of rectal lesions may be compromised by initial local excision particularly for low rectal tumours\textsuperscript{23, 27, 47, 48}. This may necessitate non restorative surgery with stoma formation.

9.1.1 Local excision

The selection criteria for cases that are suitable for local resection are not completely defined. However, local excision has the advantages of low operative mortality and morbidity together with preservation of organ function and a low stoma rate.

With local excision, the main issue is the risk of developing local recurrence. In many series this has been reported to be higher than for radical surgery\textsuperscript{39}. Recurrence rates after local excision by any method can be significant but low rates can be achieved by following guidelines such as those advocated by Bach et al 2009\textsuperscript{35} or Tytherleigh et al 2008\textsuperscript{49}. Salvage rates for local recurrence can be poor and worse results have been reported in distal rectal tumours.

9.1.2 Transanal Endoscopic Microsurgery (TEMS)

TEMS is a minimally invasive form of local excision for rectal lesions performed through a resectoscope\textsuperscript{50, 51, 52, 53, 54}. Complex polypoid lesions may be better resected by TEMS than endoscopically (EMR) as full (or partial) thickness resection of muscle can be undertaken by TEMS allowing accurate determination of T stage and sm level. This makes TEMS a treatment option for T1-Sm1/ Sm2. There may also be a place for re-excision of low risk pT1 lesions by TEMS following endoscopic polypectomy if clear margins cannot be guaranteed. TEMS may be a first line treatment for early rectal cancers in preference to endoscopic treatment if EUS suggests a depth of invasion of Sm2 or greater, there is severe dysplasia or if endoscopic appearances are not in favour of allowing a complete endoscopic resection (e.g. non-lifting during sub mucosal injection).
Appropriate patients should be entered into trials of early colorectal cancer management such as TREC. The long term results of TEMS should be judged against those of oncological resection.

9.2 The place of pre-operative adjuvant radiotherapy for rectal cancers

Preoperative adjuvant radiotherapy is addressed in recent NICE guidance\(^3\). However there is an emerging view that radiotherapy and or chemotherapy can be combined with local excision as an alternative to major surgery in early rectal cancer. Local excision of high risk (T1) lesions together with External Beam Radiotherapy (EBRT) should only be undertaken in the context of a formal clinical trial (e.g. TREC) or in a patient unfit for major radical resection or when it is the patient’s informed and objective preference.

The Papillon technique (contact radiotherapy) has been used to treat small early tumours particularly in the medically unfit\(^55\).

9.3 Oncology

At present, the place of chemo-radiotherapy in the treatment of early rectal cancer is controversial, particularly as a primary treatment in patients otherwise suitable for surgical treatment. Recent NICE guidance suggests it should not be used routinely in early disease but advocates of its use exist\(^56\). A detailed outline of emerging trends of the use of radiotherapy for rectal preservation is outside the scope of this paper. MDTs should however be aware of:

- a. the use of radiotherapy and local excision in combination;
- b. EBRT with palliative intent in the unfit patient;
- c. relevant trials that are in progress e.g. TREC (TEMS and Radiotherapy in Early Rectal Cancer).

Down staging lesions by chemo radiotherapy to ypT1 is also outside the scope of this paper.
10 The role of the MDT

Wales is formally signed up to follow NICE guidance and it is against this backdrop that the following guidance is included in this document:

a. NICE Improving Outcomes Guidance for Colorectal Cancer\(^6\) recommended the establishment of specialist early cancer MDTs on a Network basis. This advice has been reinforced by recent NICE guidance (2011)\(^3\) for Stage 1 disease.

b. Specialist MDTs are being increasingly formed in parts of the UK, which in England are subject to evaluation via the peer review programme.

MDTs should at least have access to specialist opinion as suggested by NICE\(^1\) and patient information provided. Consideration should be given to the establishment of specialist early colorectal cancer MDTs in Wales. The educational training of MDTs in the management of early cancer will be supported by the Cancer NSAG. Literature is available to help organisations develop these specialist MDTs\(^57\).

11 Follow-up

Follow up programmes, after local excision or resection, differ only in emphasis. The aim is to detect recurrence early, at a stage where further curative treatment may be possible.

After oncological resection or local excision, colonoscopic surveillance should be as for high-risk adenomas as described in BSG and European Guidelines. NICE guidance states that stage 1 colorectal cancer should be followed up with surveillance CT\(^3\).

Detection of local recurrence in rectal lesions requires special consideration. This will require endoscopy, EUS, digital exam, MRI or combinations of these and the frequency with which these need to be performed is debatable.

12 Audit

The 2009-11 audit of T1N0 cancers in Wales showed an apparently wide inter-unit variability in the management of stage 1 cancer\(^2\). Whilst the number of cases treated by each MDT was small, surgical resection rates varied between 25 and 100% following local excision\(^2\).
The reasons for this are not clear and need to be defined through audit on an all Wales basis. This can be achieved by collaboration between NBOCAP and BSW’s Quality Assurance Programme.

Central to formulating management guidelines for T1 lesions is the availability of reliable pathological data. BSW relies on Canisc but completion of the pathological fields in this is suboptimal. Although Canisc has been revised to include additional fields particularly relevant to screening (including extended laparoscopic, pathology, follow-up and complication fields) and CHIRP is being implemented, it is important that complete pathological data is prospectively collected for comparative audit. Reliable data will inform future guidelines.

Audit should also confirm the safety and appropriateness of different treatments, including surgery, against both local and national guidelines (see also implications for BSW).

### 13 Research and development

Given the lack of high level evidence on which to base management decisions, in the long term the gathering of further observational data is of paramount importance. Potential ways forward are:

- collaboration both locally and nationally in pathology studies to help establish quality assured pathology reporting of risk factors;
- entry in to trials e.g. TREC; a phase 2 trial;
- establishment of a database allowing prospective data collection and international collaboration.
14 References


Cancer NSAG summary of evidence: management of early colorectal cancer.


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Cancer NSAG summary of evidence: management of early colorectal cancer.


15 Acknowledgements

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Thanks must also go to MDTs across Wales who reviewed the document as part of a consultation prior to publication.

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Appendix 1: CHIRP reporting choices

**Polypoid cancer**
- Polyp size (in mm)
- Tumour type:
  - Adenocarcinoma
  - Other (specify)
- Differentiation:
  - Well
  - Moderate
  - Poor
- Maximum thickness from muscularis mucosae (in mm)
- Haggitt level (for polypoid tumours):
  - 1
  - 2
  - 3
  - 4
  - Into muscularis propria
  - Not applicable
- Kikuchi level (for sessile tumours):
  - sm1
  - sm2
  - sm3
  - Into muscularis propria
  - Not applicable
- Lymphatic or vascular invasion:
  - None
  - Possible
  - Definite
- Background adenoma:
  - Yes
  - No
- Margins:
  - Not involved
  - Involved by adenoma only
  - Peripheral margin involved by carcinoma
    - Distance from carcinoma to deep margin (in mm)
  - Deep margin involved by carcinoma
  - Deep and peripheral margin involved by carcinoma
  - Not assessable

**Polyp**
- Size (in mm)
- Type:
  - Tubular adenoma
  - Tubulovillous adenoma
  - Villous adenoma
  - Hyperplastic polyp
  - Serrated adenoma
  - Mixed hyperplastic polyp/adenoma
  - Inflammatory
  - Juvenile
  - Peutz-Jeghers
  - Other
    - Endocrine cell tumour (carcinoid)
    - Melanoma
    - Leiomyoma
    - Schwannoma
    - Neurofibroma
    - Ganglioneuroma
    - GIST
    - Lipoma
    - Other malignant neoplasm (specify)

**Invasive cancer (biopsy):**
- Tumour type:
  - Adenocarcinoma
  - Mucinous adenocarcinoma
  - Signet ring cell carcinoma
  - Adenosquamous carcinoma
  - Squamous cell carcinoma
  - Small cell carcinoma

**Other pathology**
- IBD - Ulcerative colitis
- IBD - Crohns
- IBD - Unclassified
- Other inflammation (description)

**Specimen site:**
- Rectum
- Rectosigmoid
- Sigmoid colon
- Descending colon
- Splenic flexure
- Transverse colon
- Hepatic flexure
- Ascending colon
- Caecum

- Normal
- Suspicious of invasive malignancy
- Inadequate
Appendix 2: Meta analysis of histopathological factors

The meta-analysis recently reported by Beaton et al analysed a cohort of 23 studies and 4510 patients. There was a significantly higher risk of lymph node metastasis with a sub mucosal invasion depth of greater than 1mm compared to lesser degrees of penetration (OR 0·387, 95% CI 1.50-10.00, p=0.005). Lymphovascular invasion was found to be significantly associated with the risk of lymph node metastasis (OR 4·81, 3·14-7·37, p<0.0001). Poorly differentiated tumours when compared to well or moderately differentiated tumours had a higher risk of lymph node metastasis (OR 5.60, 2.90-10.82, p<0.0001). Tumour budding was found to be significantly associated with the risk of lymph node metastasis (OR 7·74, 4·47-13·39, p<0·001).

The analysis concluded that in early colorectal cancer a sub mucosal invasion depth of >1mm, lymphovascular invasion, poor differentiation and tumour budding are histopathological factors that are significantly associated with a risk of lymph node metastasis. Patients who have early colorectal cancers with any one of these histopathological characteristics should be counselled regarding the risks and considered for oncological resection.
Appendix 3: Methods of risk assessment for individual patients

Each MDT needs to have a method of estimating these risks either developed locally or based on a method in the literature. The three methods outlined below are illustrative.


If there is poor differentiation, lymph vascular permeation, tumour budding or extensive submucosal invasion (Kikuchi sm3, Haggitt level 4 or width >4mm, depth >2mm), a formal colectomy or rectal resection is advised.


Egashiura et al have devised a flow chart which also includes the histopathological presence or absence and depth of a lymphatic invasion related to the adenocarcinoma.

iii) Japanese Society for Cancer of the Colon and Rectum 2010 guidelines for the treatment of colorectal cancer

The Japanese guidelines provide a literature review and consensus expert opinion. They recommend that the criteria for identifying curable T1 colorectal carcinoma after endoscopic resection are well/moderately differentiated or papillary histological grade, no vascular invasion, sub mucosal invasion depth less than 1mm and budding grade 1 (low grade).

In summary, the pathology report should inform MDT discussion on further treatment.
Appendix 4: An example of a referral pathway for early colorectal cancer

Cancer suspected at colonoscopy

- MDT
  - Biopsy
  - Surgery
  - Endoscopic Resection

Cancer in Endoscopic

- Complete Resection
  - Low Risk
    - Follow Up
- Incomplete Resection
- High Risk
  - LN
  - Co morbidity
  - MDT
    - Other e.g. DXR
    - Surgery