European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition

Management of lesions detected in colorectal cancer screening

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Keywords
- mass screening
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Multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts in a project coordinated by the International Agency for Research on Cancer. The full guideline document covers the entire process of population-based screening. It consists of 10 chapters and over 250 recommendations, graded according to the strength of the recommendation and the supporting evidence. The 450-page guidelines and the extensive evidence base have been published by the European Commission. The chapter on management of lesions detected in colorectal cancer screening includes 32 graded recommendations. The content of the chapter is presented here to promote international discussion and collaboration by making the principles and standards recommended in the new EU Guidelines known to a wider professional and scientific community. Following these recommendations has the potential to enhance the control of colorectal cancer through improvement in the quality and effectiveness of the screening process, including multi-disciplinary diagnosis and management of the disease.

Bibliography
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Background

According to the most recent estimates by the International Agency for Research on Cancer [17] colorectal cancer (CRC) is the most common cancer in Europe with 432 000 new cases in men and women reported annually. It is the second most common cause of cancer deaths in Europe with 212 000 deaths reported in 2008. Worldwide CRC ranks third in incidence and fourth in mortality with an estimated 1.2 million cases and 0.6 million deaths annually. The European Union (EU) recommends population-based screening for breast, cervical and colorectal cancer using evidence-based tests with quality assurance of the entire screening process including diagnosis and management of patients with screen-detected lesions [12]. The EU policy takes into account the principles of cancer screening developed by the World Health Organization [74] and the extensive experience in the EU in piloting and implementing population-based cancer screening programmes [69]. Screening is an important tool in cancer control in countries with a significant burden of CRC, provided the screening services are high quality [70]. The presently reported multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts and published by the EU [57].

Methods

The methods used are described in detail elsewhere in this supplement [42]. Briefly, a multidisciplinary group of authors and editors experienced in programme implementation and quality assurance in colorectal cancer screening and in guideline development collaborated with a literature group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews. The literature group systematically retrieved, evaluated and synthesized relevant publications according to defined clinical questions (modified Patient-Intervention-Comparison-Outcome-Study method). Bibliographic searches for most clinical questions were limited to the years 2000 to 2008 and were performed on Medline, and in many cases also on Embase and The Cochrane Library. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Articles of adequate quality recommended

by authors because of their clinical relevance were also included. Only scientific publications in English, Italian, French and Spanish were included. Priority was given to recently published, systematic reviews or clinical guidelines. If systematic reviews of high methodological quality were retrieved, the search for primary studies was limited to those published after the last search date of the most recently published systematic review, i.e. if the systematic review had searched primary studies until February 2006, primary studies published after February 2006 were sought. If no systematic reviews were found, a search for primary studies published since 2000 was performed.

In selected cases references not identified by the above process were included in the evidence base, i.e. when authors of the chapters found relevant articles published after 2008 during the period when chapter manuscripts were drafted and revised prior to publication. The criteria for relevance were: articles concerning new and emerging technologies where the research grows rapidly, high-quality and updated systematic reviews, and large trials giving high contribution to the robustness of the results or allowing upgrading of the level of evidence.

The methodological quality of the retrieved publications was assessed using the criteria obtained from published and validated check lists. Evidence tables were prepared for the selected studies. The evidence tables, clinical questions and bibliographic literature searches are documented elsewhere [41].

In the full guidelines document prepared by the authors and editors [57] over 250 recommendations were formulated according to the level of the evidence and the strength of the recommendation using the following grading scales.

Level of evidence:

- **I** multiple randomised controlled trials (RCTs) of reasonable sample size, or systematic reviews (SRs) of RCTs
- **II** one RCT of reasonable sample size, or 3 or less RCTs with small sample size
- **III** prospective or retrospective cohort studies or SRs of cohort studies; diagnostic cross-sectional accuracy studies
- **IV** retrospective case-control studies or SRs of case-control studies, time-series analyses
- **V** case series; before/after studies without control group, cross-sectional surveys
- **VI** expert opinion

Strength of recommendation:

- **A** intervention strongly recommended for all patients or targeted individuals
- **B** intervention recommended
- **C** intervention to be considered but with uncertainty about its impact
- **D** intervention not recommended
- **E** intervention strongly not recommended

Some statements of advisory character considered to be good practice but not sufficiently important to warrant formal grading were included in the text.

Results

Thirty-two graded recommendations are provided in Chapter 8.

Recommendations[1]

General requirements for treatment of colorectal cancer and pre-malignant lesions

8.1 Colorectal neoplasia should be managed by a multi-disciplinary team **(VI – A).**[Sect 8.2]

8.2 The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95 % of cases should be no more than 31 days **(VI – B).** [Sect 8.2]

8.3 Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding superficial lesions (see Ch. 5 [67]) **(VI – A).**[Sect 8.2; 5.1.2]

Management of pre-malignant colorectal lesions

8.4 Pre-malignant lesions detected at screening endoscopy should be removed **(III – A).**[Sect 8.3]

8.5 Lesions that have been removed should be retrieved for histological examination (see also Ch. 7 [53], Rec. 7.11) **(VI – A).**[Sect 8.3.5; 7.6.5.2; 7.8]

8.6 Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy (See Chap. 6 [60], Rec 6.13) **(V – A).**[Sect 8.3]

8.7 Large sessile lesions of the rectum should be considered for transanal surgical removal **(II – B).**[Sect 8.3.4]

8.8 For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the recommended method of local excision **(II – B).**[Sect 8.3.4]

8.9 Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V – B).**[Sect 8.3.3]

8.10 Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI – A).**[Sect 8.3]

8.11 Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V – C).**[Sect 8.3.7]

8.12 In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V – B).**[Sect 8.3.7]

8.13 In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V – B).**[Sect 8.3.7]

8.14 In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI – C).**[Sect 8.3.7]

8.15 Aspirin therapy can **(IV – C)** – and in patients with stents should – be continued prior to and during polypectomy **(VI – B).**[Sect 8.3.7]

[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation. *

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text. *

* The first digit of the section numbers and recommendation numbers refers to the respective chapter in the guidelines. For Chapter 1 to 7 see: [32, 37, 44, 23, 67, 60, 53]; for Chapters 9 to 10 see: [1, 2] respectively.

Management of pT1 colorectal cancer

8.16 If there is clinical suspicion of a pT1 cancer, a site of excision should be marked with sub-mucosal India ink **(VI – C).**[Sect 8.4.1]

8.17 Where a pT1 cancer is considered high-risk for residual disease consideration should be given to completion colectomy along with radical lymphadenectomy, both for rectal cancer **(II – A)** and colon cancer **(VI – A)**. If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7 [53], Rec. 7.7) **(VI – B).**[Sect 8.4.2; 7.5.3]

8.18 After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI – A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9 [1], Rec. 9.16) **(III – B).**[Sect 8.4.3; 9.5.1]

Management of colon cancer

8.19 If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of colectomy **(VI – B).**[Sect 8.5.1]

8.20 Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V – B).** Routine chest CT is not recommended **(III – D).**[Sect 8.5.1]

8.21 Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III – A).**[Sect 8.5.2]

8.22 Where appropriate, laparoscopic colorectal surgery should be considered **(I – A).**[Sect 8.5.2]

Management of rectal cancer

8.23 If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of excision of the rectal cancer **(VI – B).**[Sect 8.6]

8.24 Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI – B)**. Routine chest CT is not recommended **(III – D).**[Sect 8.6.1]

8.25 Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III – B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI – C).**[Sect 8.6.1]

8.26 All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II – A)** by an adequately trained specialist surgeon **(VI – A).**[Sect 8.6.3]

8.27 Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I – B).**[Sect 8.6.3]

8.28 All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I – A).**[Sect 8.6.2]

8.29 Local excision alone should only be performed for T1 sm1 rectal cancers, and if the patient is fit for radical surgery **(III – B).**[Sect 8.6.5]

8.30 In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III – B).**[Sect 8.6.5]

8.31 In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III – C).**[Sect 8.6.5]

8.32 If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II- B).**[Sect 8.6.5]

8.1 Introduction

Mortality reduction for colorectal cancer is the main endpoint of any colorectal screening programme but it must be appreciated that all screening modalities will detect substantial numbers of individuals with adenomas [34] as well as a lesser number of lesions in the serrated pathway, some of which should be treated as adenomas (see Ch. 7 [53], Sect. 7.1, 7.2 and 7.2.4).[2] As adenomas are recognised to be pre-malignant [33] screening has the potential to reduce the incidence of the disease if these lesions are adequately managed. To achieve the dual aims of mortality and incidence reduction it is essential that all the elements of the screening service achieve and maintain high levels of quality. The screening process can only be successful if it is followed by timely and appropriate management of screen-detected lesions.

In essence the management of screen-detected adenomas and carcinomas does not differ, stage for stage, from that required for symptomatic disease with the proviso that sub-optimal management can negate the benefit of screen detection. Screening does however detect a different spectrum of disease compared with that diagnosed in the symptomatic population (i.e. higher proportion of early disease) and there are some considerations in the management of screen-detected disease that should be emphasised. In this Chapter of the EU Guidelines the management of **endoscopically detected pre-malignant lesions, pT1 cancers**, as well as **colon cancer and rectal cancer** which is not limited to the submucosa are dealt with separately and discussion is focused on issues pertinent to screening. Accordingly, adjuvant chemotherapy and the management of advanced disease are not discussed.

[2] Serrated lesions can be classified as hyperplastic polyp, sessile serrated lesions, traditional serrated lesions and mixed polyps. The hyperplastic polyp must be distinguished from other serrated lesions due to its extremely low malignant potential. The significance of other lesions in the serrated spectrum is controversial and our knowledge is still developing. Hyperplastic polyps are non-neoplastic and their complete removal is optional. All other lesions in the serrated pathway should be excised and serrated lesions with neoplasia should be followed up (surveillance) as if they were adenomas (Ch. 7 [53], Sect. 7.1, 7.2 and 7.2.4, Rec. 7.10).

8.2 General requirements for treatment of colorectal cancers and pre-malignant lesions

It is widely agreed that colorectal neoplasia is best managed by a multi-disciplinary team with expertise in surgery, endoscopy, pathology, radiology, radiotherapy, medical oncology, specialist nursing, genetics and palliative care [59], working in close collaboration with primary care **(VI – A).**[Rec 8.1] The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days [47] **(VI – B).**[Rec 8.2] It should be noted that colonoscopy is not merely a diagnostic procedure, but has therapeutic capacity [11], and it is essential that the endoscopist carrying out screening colonoscopy has the necessary expertise to remove all but the most demanding polyps (see Ch. 5 [67], Sect. 5.1.2) **(VI – A).**[Rec 8.3]

Recommendations

- Colorectal neoplasia should be managed by a multi-disciplinary team **(VI – A).**[Rec 8.1]
- The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95 % of cases should be no more than 31 days **(VI – B).**[Rec 8.2]
- Colonoscopy should always be done with therapeutic intent i. e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding lesions (see Ch. 5 [67], Sect. 5.1.2) **(VI – A).**[Rec 8.3]

8.3 Management of pre-malignant colorectal lesions

(Note: the terms "pre-malignant lesion" and "polyp" are used in the following text as it is impossible to be certain of the histology of colorectal lesions prior to removal, although the intention is to treat adenomas and in some cases also serrated lesions with neoplasia or the potential to develop neoplasia, as mentioned in Section 8.1.)

There is abundant evidence that colorectal adenomas are pre-malignant [33], and it follows that a lesion found during colonoscopy that could be an adenoma should be removed **(III – A).**[Rec 8.4] Lesions should only be removed by endoscopists with adequate training in techniques of polypectomy, (see Chapter 6 [60], Rec. 6.13) **(V – A).**[Rec 8.6]

For the purposes of management, polyps may be classified as small (≤ 5 mm), pedunculated, large (≥ 10 mm) sessile colonic and large sessile rectal. Patients with large adenomas not suitable for endoscopic resection should be referred for surgical resection **(VI – A).**[Rec 8.10]

8.3.1 Small lesions

In order to obtain a representative histological specimen and to achieve definitive treatment, lesions > 5 mm are removed by snaring. Those ≤ 5 mm may be removed with biopsy forceps or cold snaring. Hot biopsy forceps may be used to ensure destruction of polyp tissue when the endoscopist is not confident about removing all the abnormal tissue with ordinary forceps. One randomised controlled trial has compared hot biopsy with cold biopsy followed by bipolar coagulation and concluded that both were equally effective and safe [51]. There is also evidence that hot biopsy is associated with a higher risk of haemorrhage than cold biopsy, particularly in the right colon [50, 73]. Cold snaring may also be used safely for polyps ≤ 6 mm [13, 66].

Lesions < 10 mm do not usually present major technical difficulties in endoscopic excision by snare electrocoagulation. It should however be born in mind that, particularly on the right side of the colon, the muscle wall is thin and even with small polyps (when they are sessile) sub-mucosal injection of saline is necessary to elevate the adenoma away from the underlying muscle wall prior to excision [11].

8.3.2 Pedunculated adenomas/polyps

The polyp on a stalk or the pedunculated adenoma is usually amenable to snare excision even when very large (≥ 20 mm) [10, 52]. In most instances it is appropriate to apply snare electro-coagulation directly to the stalk of the adenoma [14] . However, in those with thick stalks, and certainly those where the stalk is greater than 10 mm in diameter, pre-injection with 1 in 10 000 adrenaline [24] or the placement of a detachable nylon loop around the stalk below the site of coagulation [7] can reduce the risk of bleeding. There is evidence from a randomised controlled trial that pre-injection with adrenaline is effective in reducing immediate bleeding after polypectomy [24].

If after transection of the stalk arterial bleeding is seen the stalk is grasped with the diathermy loop and held (without electro-coagulation) for 5 minutes; this should at least temporarily control the bleeding. The stalk can then be injected with adrenaline and scleroscent or a nylon loop can be placed around the stalk remnant. Depending on the size and position of the stalk, the placement of one or two clips may be used as an alternative [11].

8.3.3 Large sessile colonic adenomas/lesions

With large sessile colonic lesions the choice is between formal surgical resection of the affected part of the colon and endoscopic resection at colonoscopy. The decision as to which strategy to adopt will depend on the ability of the colonoscopist and the availability of a tertiary referral centre where advanced endoscopic techniques can be used [52] **(V – B).**[Rec 8.9]

For sessile adenomas up to about 20 mm, complete excision may be possible using snare electrocoagulation after elevating the lesion by sub-mucosal injection of saline or saline plus adrenaline. The saline injection has two main functions; firstly, elevating the lesion facilitates the placement of a snare around it, and secondly, it protects the underlying muscle from damage thereby reducing the risk of perforation. For lesions > 20 mm a similar technique may be employed but piecemeal excision is necessary [15, 61], and argon plasma coagulation can be used as an adjunct to this technique in order to destroy residual adenoma tissue [5, 20]. If a lesion does not lift with sub-mucosal injection, snaring should not be attempted as this indicates involvement of the underlying muscle [11]. For large carpeting lesions, endoscopic sub-mucosal resection using elevation with saline and a specially designed sheath for the colonoscope and a needle knife may be possible [26]. It must be appreciated, however, that this is a very advanced technique and at the present time it is only available in a few specialist tertiary referral centres.

8.3.4 Large sessile rectal adenomas/lesions

While sessile rectal adenomas ≤ 20 mm in diameter may be treated by snare electro-coagulation as described for colonic adenomas, the very large carpeting lesions may be treated by surgical transanal excision **(II – B).**[Rec 8.7] For low lesions this may be

achieved using conventional transanal techniques utilising specifically designed retractors (e.g. the Pratt Bivalve Retractor, the Lone Star Retractor®). For lesions of the mid and upper rectum however where access using conventional techniques is difficult either endoscopic sub-mucosal dissection (ESD) or transanal endoscopic microsurgery (TEM) may be employed. There is evidence from a randomised controlled trial that TEM results in less local recurrence than conventional local excision [39] **(II – B).**[Rec 8.8] In some situations where there is very extensive carpeting of the rectum it may be necessary to carry out a total proctectomy. Reconstruction can then be effected by means of a hand-sewn colo-anal anastomosis.

8.3.5 Retrieval of lesions

Whenever a lesion has been removed endoscopically it should be retrieved for histological examination firstly to assess the completeness of excision and secondly to confirm the benign nature of the lesion **(VI – A).**[Rec 8.5] Under most circumstances it is feasible to trap the excised lesion using the snare and to retrieve it in this fashion. Very small polyps may be retrieved by applying suction to the biopsy channel and employing a polyp trap. When there are multiple lesions or multiple fragments of a lesion, specifically designed endoscopic retrieval bags (e.g. Rothnet®) can be employed [47].

8.3.6 Management of incomplete endoscopic excision

Incomplete excision is most common when a large sessile lesion has been removed piecemeal, but it may occur in any situation. If residual lesion tissue is seen at the time of initial polypectomy, this should be excised using snare electrocoagulation where possible. Small areas of residual tissue that are not amenable to snare electrocoagulation may be treated with direct electrocoagulation or obliteration using argon beam therapy [5, 8,55].

If there is doubt about completeness of excision at the time of initial polypectomy or if the subsequent histopathology report indicates that there may have been incomplete excision, a repeat endoscopic examination of the treated area should be carried out within 3 months. Residual abnormal tissue seen at that time can be treated as outlined above. In the situation where residual adenoma is impossible to eradicate, surgical resection of the affected part of the large bowel may be required.

8.3.7 Management of pre-malignant lesions in patients taking anti-coagulants/anti-aggregants

Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V – C).**[Rec 8.11] The existing evidence [19,25,28,29,36,63,77] relating to management of anticoagulants and antiplatelet therapy in patients undergoing endoscopic procedures is summarised in recent guidelines [68] and indicates that the use of anti-coagulants (warfarin) is associated with the significantly increased risk of bleeding after polypectomy while the use of aspirin or other NSAIDS or antiplatelet agents is not. However, the potent anti-platelet agent clopidogrel may pose a risk, especially in combination with aspirin, and although the available data are scarce, caution is advised. The following issues must be considered when deciding the management of patients taking anti-coagulants or anti-platelet therapy:

- The risk of discontinuing anti-coagulation;
- The bleeding risk associated with polypectomy;
- The morbidity and mortality rates of thromboembolic complications versus those of bleeding complications; and
- The timing of cessation and reinstitution of anti-coagulants or anti-platelet therapy.

Warfarin is discontinued 3 to 5 days before the procedure. Patients at high-risk of thromboembolic events receive subcutaneous low-molecular-weight-heparin (LMWH) which is stopped at least 8 hours before the procedure. The LMWH can be resumed 6 hours after the procedure.

Another option is to perform an initial diagnostic colonoscopy followed if necessary by a second colonoscopy for polypectomy using LMWH bridge therapy. If the high-risk of thromboembolism is potentially transient (e.g. deep venous thrombosis), the best option is to delay the polypectomy until the risk is decreased.

Ideally, and certainly until further evidence is available relating specifically to polypectomy, individuals taking clopidogrel must stop this medication at least 7 days before polypectomy is performed where it is safe to do so. However, in patients with coronary stents, stopping clopidogrel within 1 month for bare stents and within 12 months for drug-eluting stents carries a high-risk of acute thrombosis of the stent and myocardial infarction. In patients such as these, endoscopic polypectomy must be delayed for the appropriate period of time **(V – B).**[Rec 8.12; 8.13] In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI – C).**[Rec 8.14] Aspirin therapy can **(IV – C)** – and in patients with stents should – be continued **(VI – B).**[Rec 8.15]

8.3.8 Synopsis

Summary of evidence

- Colorectal adenomas are recognized as pre-malignant **(III).**
- Colonic adenomas can be removed by biopsy forceps, cold snaring, electrocoagulation snares or, when large and sessile, by endoscopic sub-mucosal resection **(V).**
- Rectal adenomas, when not suitable for colonoscopic excision, can be removed by surgical transanal excision with or without the use of transanal endoscopic microsurgery (TEM) or endoscopic sub-mucosal dissection (ESD) **(II).**
- Large colonic or rectal adenomas can be treated by surgical resection of the affected area if endoscopic resection is not possible **(V).**
- The use of sub-optimal technique for polypectomy can result in perforation with attendant morbidity and mortality **(V).**
- Removal of adenomas in an anticoagulated patient can result in potentially fatal haemorrhage **(V).**
- Stopping clopidogrel within 1 month of the placement of bare coronary stents can result in acute thrombosis of the stent and myocardial infarction **(III).**
- Stopping clopidogrel within 12 months of the placement of drug-eluting coronary stents can result in acute thrombosis of the stent and myocardial infarction, **(III)** although if absolutely essential it *may* be stopped temporarily at 6 months **(IV).**

Recommendations for management of colorectal pre-malignant lesions

- Pre-malignant lesions detected at screening endoscopy should be removed **(III – A).**[Rec 8.4]
- Lesions that have been removed should be retrieved for histological examination **(VI- A).**[Rec 8.5]
- Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy **(V – A).**[Rec 8.6]

- Large sessile lesions of the rectum should be considered for transanal surgical removal **(II – B).**[Rec 8.7]
- For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the preferred method of local excision **(II – B).**[Rec 8.8]
- Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V – B).**[Rec 8.9]
- Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI – A).**[Rec 8.10]
- Appropriate precautions should be taken prior to endoscopic excision in patients on anticoagulants **(V – C).**[Rec 8.11]
- In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V – B).**[Rec 8.12]
- In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V – B).**[Rec 8.13]
- In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI – C).**[Rec 8.14]
- Aspirin therapy can **(IV – C)** and in patients with stents should – be continued prior to and during polypectomy **(VI – B).**[Rec 8.15]

8.4 Management of pT1 cancers

8.4.1 Primary management

A pT1 cancer can be defined as an invasive cancer that is confined to the submucosa. pT1 cancers are also commonly referred to as polyp cancers because they are generally detected and removed endoscopically. Although the evidence base relating to the management of these lesions is weak [4, 9, 16, 18, 22], there has been one narrative review of this subject, and the recommendations given here are derived from the evidence cited in this review [43].

The primary management of a pT1 cancer is, by definition, identical to that of an adenoma (see Sect. 8.3). In most cases the diagnosis of pT1 cancer is made on histological examination of the endoscopically excised lesion but the following features raise the suspicion of a polyp cancer:

- Lesion is larger than 20mm;
- Lesion is uncharacteristically hard; or
- Lesion is ulcerated.

Identification of a previous polypectomy site may be difficult and can cause problems for the surgeon in deciding on the anatomical region to be removed if completion surgery (see below) is required. This problem can be overcome by injecting India ink sub-mucosally at the site of a suspected pT1 cancer at the time of its removal **(VI – C).**[Rec 8.16] India ink tattooing should be performed distal to the lesion and include at least three quadrants of the bowel. Care should be taken to avoid "Indian ink peritonitis" by initial raising of the mucosa with saline.

pT1 cancers can be categorised into low-risk and high-risk lesions according to their likelihood of being associated with lymph node metastases:

- Low risk: Well or moderately differentiated and no lymphovascular invasion; rate of lymph node metastases < 5 %
- High risk: Poorly differentiated and/or lymphovascular invasion; rate of lymph node metastases ~35 %

The significance of venous invasion is currently unknown.

8.4.2 Completion surgery

Patients with a histologically confirmed, completely removed low-risk pT1 cancer do not require additional surgery, due to their low risk of lymph node metastases. In patients with a high-risk polyp cancer with clear margins (RO), the multidisciplinary team should be consulted on whether completion surgery involving removal of the part of the large bowel in which the polyp was situated, along with radical lymphadenectomy, for both rectal cancer **(II – A)** and colon cancer **(VI – A)** is recommended.[Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist, as variation exists in evaluating high-risk features (See also Ch. 7 [53], Sect. 7.5.3 and Rec. 7.7) **(VI – B).**[Rec 8.17] The precise nature of the surgery will of course depend on the site of the pT1 cancer. It may be difficult to precisely locate the site of the previous polypectomy and for this reason inking of the site at the time of initial polypectomy is advised when there is any clinical suspicion of polyp cancer (see above).

It should be noted that if a suspected pT1 cancer has been *incompletely* removed, lack of invasion beyond the submucosa cannot be guaranteed, and thus even in the situation where the lesion is well or moderately differentiated with no lymphovascular invasion, further treatment is required. This will usually take the form of completion surgery, although repeat endoscopic excision may be possible and appropriate in some situations.

In summary, current consensus would classify a pT1 cancer as high-risk requiring completion surgery in the following circumstances:

- When invasive cancer is seen at or within 1 mm of the resection margin;
- Where the cancer is poorly differentiated; or
- Where there is evidence of lymphovascular invasion within the resected specimen.

8.4.3 Follow-up

After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI – A).**[Rec 8.18] After removal of a low-risk pT1 cancer, many endoscopists consider the surveillance policy employed for high-risk adenomas to be appropriate follow-up (see Ch. 9 [1], Sect. 9.5.1, Rec. 9.16) **(III – B).**[Rec 8.18] In the case of removal of a high-risk pT1 cancer without additional completion surgery for whatever reason, a more intensive programme of follow-up would be appropriate because of the increased risk of cancer recurrence. It is suggested that such patients benefit from quarterly endoscopic inspection of the polypectomy site for 1 year and then bi-annual inspection for a further 2 years. After this, the surveillance protocol for high-risk adenomas can be adopted. Given the increased risk of extramural recurrence in patients with high-risk pT1 cancers without completion surgery, it is also appropriate to use cross-sectional imaging of the abdomen on a bi-annual basis for a period of 3 years.

8.4.4 Synopsis

Summary of evidence

- When invasive cancer is present in a polypectomy specimen, the risk of residual disease is associated with distance from the resection margin, degree of differentiation and degree of lymphovascular invasion **(III).**

- The precise site of a polyp within the colon is difficult to define at colonoscopy **(VI).**

Recommendations for management of pT1 cancers

- If there is clinical suspicion of a pT1 cancer a site of excision should be marked with sub-mucosal India ink **(VI – C).**[Rec 8.16]
- Where a pT1 cancer is considered high-risk for residual disease, consideration should be given to completion colectomy along with radical lymphadenectomy, for both rectal cancer **(II – A)** and colon cancer **(VI – A).**[Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7 [53], Sect. 7.5.3 and Rec. 7.7) **(III – A).**[Rec 8.17]
- After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI – A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9 [1], Sect. 9.5.1, Rec. 9.16) **(III – B).**[Rec 8.18]

8.5 Management of colon cancer

The management of screen-detected colon cancer is not materially different from that of the management of symptomatic cancer. Management of pT1 colon cancer has been dealt with in Section 8.4. The following summary deals with management of colon cancer which is not limited to the submucosa; it is derived from evidence based guidelines [31, 45,48,56,59].

8.5.1 Preoperative staging

Once the diagnosis of colon cancer has been made (usually by means of colonoscopic biopsy) it is essential to a) ensure that the whole colon has been visualised for second primaries or adenomas and b) screen the patient for metastatic disease.

The reason for visualising the whole colon is that 5% of patients with a colorectal cancer will have a synchronous cancer, and more will have adenomas that require removal.

If a complete colonoscopy has not yet been performed, either because the primary lesion precluded total colonoscopy or any other reason, the rest of the colorectum should be visualised radiologically before surgery, if at all possible. This should be performed ideally by CT colography, or if this is not available, by high quality double contrast barium enema. If for any reason the entire colon is not visualised prior to surgery then a complete colonoscopy should be carried out within 3 to 6 months of excision of the colon cancer **(VI – B).**[Rec 8.19]

In terms of screening for metastatic disease, patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V – B).** Routine chest CT is not recommended **(III – D).**[Rec 8.20]

8.5.2 Surgery

As with all patients with colon cancer, the quality of surgery for screen-detected cancers is central to the outcome. Safe, high-quality surgery is essential for screen-detected cancers given that surgery-related mortality will result in greater shortening of life for patients with screen-detected cancers compared with those with symptomatic cancers.

The exact nature of the colectomy will of course depend on the anatomical location of the tumour but in general terms the most common operations will be a right hemicolectomy for tumours in the caecum or ascending colon, an extended right hemicolectomy for tumours in the transverse colon up to the splenic flexure, a left hemicolectomy for tumours between the splenic flexure and the sigmoid colon and a sigmoid colectomy for tumours of the sigmoid colon.

There is accumulating evidence that radicality of surgery is associated with better long-term outcomes and it is recommended that all of these operations be carried out with a full lymphadenectomy that involves flush ligation of the feeding vessels at the superior mesenteric artery or aorta as appropriate [72]. There is also increasing evidence that outcomes after surgery for colon cancer, both short- and long-term, are dependent on the degree of specialisation and experience of the surgeon [38]. Thus patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III – A).**[Rec 8.21]

Increasingly, laparoscopic surgery is being used to treat colon cancer, and screen-detected colon cancer is often amenable to this approach. The evidence suggests that advantages of laparoscopic surgery are related to short-term rather than long-term outcomes, but randomised controlled trials indicate that it is oncologically safe [30]. Thus where appropriate, laparoscopic colorectal surgery should be considered **(I – A).**[Rec 8.22] However, it is essential that if laparoscopic surgery is employed, the oncological principles outlined above are adopted. It is also essential that the surgeons carrying out laparoscopic surgery be fully trained in this technique.

8.5.3 Synopsis

Summary of evidence

- High-quality surgery is the optimal primary treatment for colon cancer **(III).**
- In appropriately selected patients laparoscopic colon cancer surgery can offer better short-term outcomes **(I).**

Recommendations for management of colon cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of colectomy **(VI – B).**[Rec 8.19]
- Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V – B).** Routine chest CT is not recommended **(III – D).**[Rec 8.20]
- Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III – A).**[Rec 8.21]
- Where appropriate, laparoscopic colorectal surgery should be considered **(I – A).**[Rec 8.22]

8.6 Management of rectal cancer

The management of screen-detected rectal cancer is not materially different from that of the management of symptomatic rectal cancer. Management of pT1 rectal cancer has been dealt with in Section 8.4. The following summary deals with management of rectal cancer which is not limited to the submucosa; it is derived from evidence based guidelines [21, 46, 56, 59, 64]. However, the

issue of how to treat small rectal cancers that are technically suitable for local excision is particularly germane to screen-detected disease, and particular emphasis is placed on this area.

8.6.1 Pre-operative staging

Pre-operative staging considerations are the same as those for colon cancer, including visualisation of the entire colon, (see Section 8.5.1 and Recommendations 8.19 and 8.20).[Rec 8.23; 8.24] In addition, however, it is important that the primary tumour be imaged in order to assess the need for neoadjuvant therapy. It is recommended that MRI of the pelvis be carried out for this purpose **(III – B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI – C).**[Rec 8.25] It should also be borne in mind that large rectal adenomas may harbour invasive malignancy, and it is recommended that all of these should be evaluated pre-operatively by transrectal ultrasound in order to assess the likelihood of possible invasive malignancy. Endoscopic ultrasound may also be helpful in distinguishing T1 from T2 tumours.

8.6.2 Neoadjuvant therapy

For many years it has been recognised that adjuvant radiotherapy given either pre-operatively or post operatively reduces the risk of local recurrence after radical excision of rectal cancer. There is now good evidence that pre-operative treatment is superior to post-operative treatment [46, 59] and it follows that all patients with rectal cancer (and certainly those predicted on imaging to have T3 /4 cancers and/or lymph node metastases) should be considered for pre-operative radiotherapy with or without concomitant chemotherapy **(I – A).**[Rec 8.28] It is not possible to be prescriptive regarding the regime as this is dependant on pre-operative assessment of the individual tumour, the fitness of the patient (particularly with regard to chemotherapy), and on local protocols.

8.6.3 Surgery

Radical surgery for rectal cancer consists of either anterior resection or abdomino-perineal excision of the rectum. The latter operation is reserved for tumours where it is impossible to mobilise the tumours sufficiently to achieve an anastomosis, and in specialist practice this accounts for less than 40 % of all rectal cancers. The main principle of rectal cancer surgery is to obtain an adequate circumferential margin clearance of the tumour and to this end all rectal cancers treated by radical surgery are best served by the technique of mesorectal excision **(II – A).**[Rec 8.26] In cancers of the upper rectum it is acceptable to transect the mesorectum 50 mm distal to the tumour, but in cancers of the lower two thirds, total mesorectal excision is required. Evidence is accumulating that when an abdomino-perineal excision is carried out, wide excision of the pelvic floor is required to obtain adequate tumour clearance [71].

There is now very good evidence that the quality of the surgery is strongly correlated with local recurrence and survival [54], and, as with colon cancer, both short- and long-term outcomes are dependent on the degree of specialisation and experience of the surgeon [38]. Therefore all patients undergoing radical surgery for rectal cancer should have mesorectal excision by an adequately trained specialist surgeon **(VI – A).**[Rect 8.26]

The same general considerations regarding laparoscopic surgery for colon cancer apply to rectal cancer (see Sect. 8.5.2 and Rec. 8.22) **(I – B).**[Rec 8.27] It should be considered, however, that a recent Cochrane Review concluded that laparoscopic surgery for the upper rectum is feasible, but more randomised trials are required to assess the long-term outcome [30].

8.6.4 Post-operative radiotherapy

Post-operative radiotherapy plus concomitant chemotherapy is indicated when a rectal tumour has been removed without pre-operative radiotherapy and where the resection margins are threatened by invasive cancer [40, 49,58] **(III)**.

8.6.5 Management of small rectal cancers

A major effect of a screening programme is to increase the number of small primary cancers that are diagnosed, and because the rectum can be accessed transanally this opens up the possibility of local excision for small rectal cancers. This can be achieved using conventional approaches with specifically designed retractors (e. g. the Pratt Biovalve Retractor and the Lone Star Retractor) or, if the tumour is in the mid- or upper rectum, using transanal endoscopic microsurgery (TEM) [65]. If a decision is made to locally excise a proven rectal cancer, this must be done along with an underlying full-thickness disk of rectal muscle and a margin of normal tissue of at least 5 mm in order to maximise the chance of complete excision. It must be recognised that this is only suitable for posterior rectal tumours or low anterior rectal tumours. A full-thickness excision of a high anterior rectal tumour, particularly in a female, can result in perforation into the peritoneal cavity.

The main issue surrounding local excision of early rectal cancers is the risk of recurrence, and the evidence is such that most surgeons consider the risk of local recurrence after local excision to be considerably higher than that after radical rectal excision [65]. The risk of recurrence is dependent on the depth of invasion of the primary tumour, tumour diameter, lymphovascular invasion and degree of differentiation [3]. T2 tumours are associated with at least a 20 % risk of recurrence after local excision [76]; T1 tumours are associated with a lesser risk of local recurrence, but again this is dependent on the depth of invasion. Kikuchi sm1 level tumours (superficial one third of the sub-mucosa) are associated with a negligible risk of local recurrence and can be safely treated by local excision [27]. Kikuchi level sm2 tumours (superficial two thirds of sub-mucosa) are associated with an 8 % risk of local recurrence, and Kikuchi level sm3 tumours (full thickness involvement of the sub-mucosa) are associated with almost the same risk of local recurrence as T2 tumours. Thus under most circumstances radical surgery for sm2 and sm3 tumours is indicated. If a local excision is made and the pT stage is T1 sm3 or worse then radical excision should be carried out provided the patient is fit enough for radical surgery **(II – B).**[Rec 8.32]

There is, however, a school of thought that local excision combined with radiotherapy plus or minus chemotherapy may produce acceptable local recurrence rates in T1, T2 and even T3 tumours; however the evidence to support this comes from relatively small case series. A recent review of the literature examined the use of pre-operative chemoradiation (CRT) and local excision, and found that local recurrence was 0 % for those with pT0 tumours (i. e. complete response to CRT), 2 % for pT1 tumours, 7 % for pT2 tumours and 21 % for pT3 tumours [6]. (Note: in this context, pT refers to the *histopathological* T stage determined on the resection specimen after CRT).

There have been two RCTs comparing local excision by means of TEM and radical resection. One compared TEM alone with radical resection for T1 carcinoma [75], and the other compared TEM

plus pre-operative CRT with radical surgery for T2 tumours [35]. Both demonstrated significantly shortened operating times, less blood loss, less analgesic usage and shorter duration of hospitalisation with the TEM approach, but although neither demonstrated a difference in local recurrence rates, neither trial was sufficiently powered to examine this outcome.

In summary, with the exception of sm1 T1 cancers, there is a significant risk of local recurrence after local excision, although this may be modified by pre-operative CRT.

This view is supported by two recent systematic reviews [39, 62]. Therefore, local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is fit for radical surgery **(III – B).**[Rec 8.29] Furthermore, in patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III – C).**[Rec 8.31]

If however there is doubt about the fitness of the patient for radical surgery, local excision of more advanced rectal cancer could be considered **(III – B).**[Rec 8.30]

8.6.6 Synopsis

Summary of evidence

- The quality of surgery for rectal cancer, particularly with respect to circumferential margin involvement and the plane of surgery are strongly associated with outcome in terms of local recurrence and survival **(III)**.
- Although the evidence is not as extensive as for colon cancer, there is evidence that laparoscopic surgery for rectal cancer may be associated with better short-term outcomes without significant detriment **(I)**.
- Preoperative radiotherapy is associated with improved local recurrence rates and improved survival in appropriate patients undergoing radical surgery for rectal cancer **(I)**.
- Although small rectal cancers can be excised locally, local recurrence rates are higher than with radical surgery, with the exception of early (sm1) T1 cancers **(III)**.
- If a rectal cancer can be downstaged to pT0 or pT1 with CRT, local excision is associated with low local recurrence rates **(V)**.

Recommendations for management of rectal cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of excision of the rectal cancer **(VI – B).**[Rec 8.23]
- Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI – B).** Routine chest CT is not recommended **(III – D).**[Rec 8.24]
- Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III – B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI – C).**[Rec 8.25]
- All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II – A)** by an adequately trained specialist surgeon **(VI – A).**[Rec 8.26]
- Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I – B).**[Rec 8.27]
- All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I – A).**[Rec 8.28]
- Local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is not fit for radical surgery **(III – B).**[Rec 8.29]
- In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III – B).**[Rec 8.30]
- In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III – C).**[Rec 8.31] If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II – B).**[Rec 8.32]

Conclusions

In a multidisciplinary process, wide consensus has been achieved on a comprehensive package of evidence-based recommendations for quality assurance in management of lesions detected in colorectal cancer screening. Following these recommendations has the potential to enhance the control of colorectal cancer in Europe and elsewhere through improvement in the quality and effectiveness of the screening process that extends from systematic invitation to management of screen-detected cases.

Disclaimer

The views expressed in this document are those of the authors. Neither the European Commission nor any person acting on its behalf can be held responsible for any use that may be made of the information in this document.

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