National Institute for Health and Care Excellence

IP1724 Low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced rectal cancer (IPG659)

IPAC date: 10/09/20

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS professional	**General**	I have been nominated by Association of Coloproctology and was appointed by NICE as their specialist advisor for the above review in March 2019. I submitted my views in response to the questionnaire sent. However, I or any of the other advisors has been asked to comment on the IPG 659 recommendations before it was published on 14th August 2019. I have been appointed by NICE twice as their specialist advisor on rectal brachytherapy (2006, 2015) and usually we were asked to review the draft recommendations for accuracy and scientific facts stated in their documents before they were published. I was not asked to review IPG 659. It may be that you have changed your policy. However, I would like to point out that there are some errors and inaccuracies of facts in this document published.	Thank you for your comments. There has been no change to NICE policy or process in producing guidance and the NICE IP team apologises for the fact you were not previously asked to comment which was due to a communication error. NICE withdrew the guidance and a second public consultation was held and completed by August 2020. Consultation comments received and additional literature (found as part of an update search) has been considered at IPAC in September 2020.
2	Consultee 1 NHS professional	**1.1**	1. IPG659 recommendation stated that “Current evidence on the safety and efficacy of low-energy contact X-ray brachytherapy (the Papillon technique) for locally advanced rectal cancer is inadequate in quantity and quality”. **This statement is not correct.** Safety for CXB (Papillon) has been reviewed in depth and reported in the previous NICE recommendation for early rectal cancer (IPG 532) which stated that “In patients for	Thank you for your comments. IPAC considered your comments but decide not to amend section 1.1 in the guidance. The committee considered that the safety profile of the procedure could be different in advanced rectal cancer compared to early rectal cancer (for

			whom surgery is not considered suitable, current evidence on the efficacy and safety of low-energy contact X-ray brachytherapy (CXB; the Papillon technique) for early-stage rectal cancer is adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance, consent and audit". 1. **Safety** - Safety of CXB cannot be different for either advanced or early staged rectal tumours. The type of radiation use is low energy radiation (50 KeV), the dose (90-110Gy), fractionation (3-4 fractions) and the treatment volumes use are exactly the same for both early and advanced rectal cancers. Therefore, toxicity due to CXB (on surrounding normal tissue) is exactly the same whether the treated tumour is early or in advanced stages. Side effects resulting from the radiation to the surrounding normal tissues using the same dose and fractionation cannotg be different. **Therefore, IPG 659 statement should not contradict IPG 532 statement that safety information on CXB is inadequate in quantity and quality.**	example the rectum may have been exposed to external beam radiotherapy and chemo/radiotherapy may have been administered). This underpinned the committee's request for the need for further research into the safety of this technique in advanced rectal cancer.
3	Consultee 1 NHS professional	**1.1**	2. **Efficacy** - The response to treatment can be different with early tumour responding better than more advanced ones. However, for advanced stage rectal cancer, we usually start with external beam radiotherapy (EBRT) or external beam chemo radiotherapy (EBCRT) and only offer CXB in patients who responded to external beam radiotherapy. Therefore, we select out good responder from the poor responders. Poor responders are usually persuaded to accept surgery although they may not be keen on having a stoma. We offer no further treatment if the patient achieve a true clinical complete response (cCR) [10-20%]. We only offer CXB to small residual tumour (<3cm) to achieve better local control in patient who are not suitable for surgery or refusing surgery as they are stoma phobic. At this stage the residual tumour is either pT1 or pT2. Published data from TEMS following EBCRT or SCRT showed that residual tumour is either pT0, pT1 or pT2 and not the same stage as their original tumour	Thank you for your comments. References 5,6,7 are already included in table 2 in the overview. The study by Gerard 2004 has been added to the appendix in the overview as outcomes of this group of patients are reported in the Ortholan 2012 study which is included in table 2 in the overview. IPAC considered your comments but decided not to amend 1.1.

			cT3 [1, 2]. Therefore the response for these down staged tumours are exactly the same as that of early stage tumours and cannot be different. The efficacy of CXB is not different in either early stage (treated upfront) or down staged tumours (after EBCRT). This is important especially for patients not suitable for surgery as residual tumour if not treated will regrow and relapse (80-90%). 3. IPG 659 should include the status of patient which is suitable for surgery or not suitable for surgery. If the patient with advanced rectal cancer is not suitable for surgery, usually EBCRT or EBRT is only offered. There is published evidence from large cohort of international patients reported on 10% of pCR in those who had surgery after EBCRT for advanced rectal cancer [3, 4]. Therefore, if there is residual tumour (90%) after EBCRT or EBRT the majority of these patients (who are not suitable for surgery) cannot have salvaged surgery as they are older, frail and not fit. This is the group who will benefit most if CXB is offered for their residual cancer. There is published evidence for the benefit of CXB boost in improving initial cCR rates to 70-80% and reducing the local regrowth from 30% to less than 11%. Therefore, statement of efficacy of CXB is inadequate is not correct [5, 6, 7]. We cannot do a randomised trial in patients who are not suitable for surgery. However, there was published evidence of CXB efficacy in addition to EBRT from a randomised trial Lyon 96-02 in patients who were fit for surgery [8]. **References** 1. Smart CJ, Korsgen S, Hill J, Speake D, Levy B, Steward M, et al. Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer. Br J Surg 2016; 103: 1069–75. https://doi.org/10.1002/bjs.10171 2. Verseveld M, de Graaf EJ, Verhoef C, van Meerten E, Punt CJ, de Hingh IH, et al. Chemoradiotherapy for rectal	

			cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). Br J Surg 2015; 102: 853–60. https://doi.org/10.1002/bjs.9809 3. The 2017 European Society of Coloproctology (ESCP) Collaborating Group. Evaluating the incidence of pathological complete response in current rectal cancer practice: the barriers to widespread safe deferral of surgery Colorectal Dis 2018; 20(suppl. 6): 58–68. https://doi.org/10.1111/codi.14361. 4. Sun Myint A, Dhadda A, Rao C et al. Letter to editor in response to: - Re: Evaluating the incidence of pathological complete response in current international rectal cancer practice: the barriers to widespread safe deferral of surgery. Colorectal Disease 2019; https://doi.org/10.1111/codi.14472 5. Sun Myint A, Smith F, Gollins S et al. Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: Does it improve the chance of organ preservation? B J Radiology (2017); 90: 2017017. https://doi.org/10.1259/bjr.20170175. 6. Dhadda AS, Martin A, Killeen S, Hunter IA. et al. Organ preservation using contact radiotherapy for early rectal cancer: Outcomes of patients treated at a single centre in the UK. Clin Oncol 2017; 29:198–204. https://doi.org/ 10. 1016/ j.clon.2016. 09. 014. 7. Frin AC, Evesque L, Gal J, Benezery K, Francois E, Gugenheim J, et al. Organ or sphincter preservation for rectal cancer. The role of contact X-ray brachytherapy in a monocentric series of 112 patients. Eur J Cancer 2017; 72: 124–36. https://doi.org/10.1016/j.ejca.2016.11.007 8. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the Lyon R96-02 randomized trial. J Clin Oncol 2004; 22: 2404–9. https://doi.org/10.1200/JCO.2004.08.170	

4	Consultee 1 NHS professional	**Other**	7. In IPG 659 recommendations, there was no mention of Health economic assessment papers published for CXB compared to surgery [12, 13]. There are two published papers on Health economics of Papillon which were not considered in your report. **References:** 12. Rao C, Smith F, Martin AP. A Cost-Effectiveness Analysis of Contact X-ray Brachytherapy for the Treatment of Patients with Rectal Cancer Following a Partial Response to Chemoradiotherapy. Clinical Oncology 2017. **https://doi.org/10.1016/j.clon.2017.11.015** 13. Rao C, Stewart A, Martin AP, et al. Contact X-ray Brachytherapy as an Adjunct to a Watch and Wait Approach is an Affordable Alternative to Standard Surgical Management of Rectal Cancer for Patients with a Partial Clinical Response to Chemoradiotherapy. Clinical Oncology 2018; **https://doi.org/10.1016/j.clon.2018.06.010**.	Thank you for your comments. Costs are out of the remit of the IP programme so these papers have not been considered in our evidence assessment.
5	Consultee 1 NHS professional	**Committee comments, section 3.5 FIPD**	8. Committee comments on the patients' commentaries "The committee was pleased to receive a large number of patient commentaries which were positive but also reported highly unpleasant short-term side effects" is not fair as most patients were satisfied with their treatment and their outcomes. No patients reported highly unpleasant short term side effects in their response to the questionnaire yet it was stressed in the committee comments as a significant side effects. Most if not all patients were grateful to avoid surgery and a stoma. Lots of comments about surgeons not giving them a choice for their treatment and they have to find out about Papillon themselves. One patient used the term 'Bullied into surgery'. As the results of your IPG 659 recommendation, many patients will be bullied to accept surgery which they don't want. The recommendations from GMC (good practice guide) stated to work in partnership with patients. ● Listen to, and respond to, their concerns and preferences.	Thank you for your comments. IPAC considered your comments and amended wording in committee comment 3.5 in the guidance.

			● Give patients the information they want or need in a way they can understand. ● Respect patients' right to reach decisions with you about their treatment and care. ● Support patients in caring for themselves to improve and maintain their health. NICE colorectal guideline (2011) recommend that: - • Before starting treatment, offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments including the effect on bowel function. Yet, many patients commented that no information on alternative treatment was given to them by the surgical team responsible who felt that there was no evidence of safety and efficacy for alternative treatments. IPG 659 recommendation will bias the treatment that are available especially for patients with advanced rectal cancer who are not suitable for surgery. Many older patients and those not suitable for surgery will be harmed and disadvantage by IPG659 recommendation. Many will be bullied by their surgical team to accept surgery as 'the standard of care' for those who are fit for surgery against their wishes.	
6	Consultee 2 NHS professional President, International Contact Radiotherapy Group Network	**1.1**	My final comment is that guidance IPG 659 cannot contradict the earlier guidance IPG 532 with regards to the safety of the contact brachytherapy procedure. I cannot see how there can be new issues with regards to safety with the new guidance when no new publications documenting increased toxicity have been published in the intervening period.	Thank you for your comments. IPAC considered your comment but decided not to amend 1.1 in the guidance. The committee considered that the safety profile of the procedure could be different in advanced rectal cancer compared to early rectal cancer (for example the rectum may have been exposed to external beam radiotherapy and chemo/radiotherapy

				may have been administered). This underpinned the committee's request for the need for further research into the safety of this technique in advanced rectal cancer.
7	Consultee 1 NHS professional	**2.1**	5. The statement in IPG 659 stating that "between 5% and 10% of patients present with locally advanced disease (stage T3b to T4)" is not correct. It is difficult to define the advanced stage cancer. 'T' stage is not the only parameter that can be used. 'N' stage is also important and approximately 26% of rectal cancer are Dukes 'C' and most clinicians regard Dukes C patients as advanced stage as they are more likely to develop local recurrence and distant metastases. Similarly, CRM involvement (on MRI) is also an important factor regardless of the 'T 'stage as these patients with involved CRM are likely to relapse. Therefore, at least 26 % of rectal cancer patients presented at the advanced stage [10]. **References:** 10. Colorectal cancer: the diagnosis and management of colorectal cancer. Clinical guideline. NICE (2011). **https://www.nice.org.uk/guidance/cg131**	Thank you for your comments. IPAC considered your comments and amended 2.1 in the guidance
8	Consultee 1 NHS professional	**2.1**	*'5% and 10% of patients present with locally advanced disease (stage T3b to T4)'.* It is difficult to define locally advanced rectal cancer Usual definitions include 1. CRM (+) tumours 2. Spread to the lymph nodes (cN1 or cN2). Once the lymph nodes are involved the stage becomes III even though T stage may be cT1 or cT2 and these are regarded as poor prognostic group tumours. Therefore, locally advanced rectal cancer could be more than 5-10%. This statement is incorrect and should be removed.	Thank you for your comments. IPAC considered your comments and amended 2.1 in the guidance.
9	Consultee 1 NHS professional	**2.2**	6. In the current treatment option it was stated that "In patients who elect not to have surgery, or are not fit enough to have it, local surgical resection with systemic or radiation	Thank you for your comments.

			therapies, or both may be given". **This is not correct.** In the current national colorectal guidelines TEMS is recommended only for early pT1 tumours and not for advanced rectal cancer [11]. Moreover, TEMS resection needs general anaesthesia and patients who are not fit for surgery cannot have TEMS. EMR or transanal resection (TART) under sedation are not suitable for advanced rectal cancer (T3 or T4). **Therefore, this statement is not correct.** References 11. Simon Gollins, Brenden Moran, Richard Adams et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus– Multidisciplinary Management. Guidelines for management of colorectal cancer. Colorectal Disease. 2017; 19(1):1-97. **https://www.acpgbi.org.uk/resources/guidelines-management-cancer-colon-rectum-anus-2017/**	IPAC considered your comments and amended 2.2 in the guidance.
10	Consultee 1 NHS professional	**2.2**	*'local surgical resection'* Should remove this statement from your guidance as local surgical resection for locally advanced rectal is not only inappropriate but contraindicated. There is no published evidence for local surgical resection combine with systemic treatment for locally advanced rectal cancer. This should also be removed from your statement. There is published evidence for combined radiotherapy and chemotherapy in CRM (+) locally advanced rectal cancer. Not chemotherapy on its own or radiotherapy on its own. The aim is to reduce the tumour size, alleviate symptoms and improve quality of life.	Thank you for your comments. IPAC considered your comments and amended 2.2 in the guidance.

			This statement suggest that curative treatment cannot be achieved without surgery. This statement is bias and should be removed. There is international watch and Wait data base which showed better survival and QOL without surgery. International Watch and Wait data base (IWWD) has published long term cure and survival data on 880 patients treated with EBCRT alone without surgery (Van der Valk et al 2018, Lancet) There is published evidence from International Watch and wait database [IWWD] (Maxime J M van der Valk (2018) Lancet) on non-surgical treatment of locally advanced rectal cancer on 880 patients. More than half of these patients were either cT3 or cT4 (54%) who received EBCRT and achieved a long term clinical complete response (cCR) and eventual cure. Therefore, your statement that nonsurgical treatment with chemoradiotherapy aims only to reduce tumour size, alleviate symptoms and improve QOL is not correct.	
11	Consultee 2 NHS professional President, International Contact Radiotherapy Group Network	**2.2**	I wish to make some comments on the above NICE guidance in my capacity as the current President of the International Contact Radiotherapy Network, of which 4 UK Centres are active members (Liverpool, Hull, Nottingham and Guildford). Firstly, there is no question that in fit patients the gold standard treatment for locally advanced rectal cancer is radical surgery in the form of a TME, potentially preceded by neo-adjuvant chemo/radiotherapy. However, the guidance as worded would potentially be to the detriment of patients who are unfit for surgery and who have had a good response to initial external beam radiotherapy treatment. There is level 1 evidence from the Lyon 96-02 trial (Gerard J et al 2004, Ortholan C et al 2012) that the addition of a contact brachytherapy boost to external beam radiotherapy increases response and sphincter preservation. Although it was not initially designed to look at the endpoint of organ preservation, there were patients in the brachytherapy arm	Thank you for your comments. IPAC considered your comments and amended 2.2 in the guidance. The study by Ortholan 2012 has been added to table 2 in the overview. The study by Gerard 2004 has been added to the appendix in the overview. The outcomes of this group of patients are reported in the Ortholan 2012 study which is included in table 2.

			who ultimately refused radical surgery and achieved long term organ preservation (6/45 patients). Colostomy free survival at 10 years was 71% vs 37% with the addition of the contact brachytherapy boost. Hence, in unfit patients showing a response to external beam treatment it is likely a brachytherapy boost, if appropriate and technically feasible, would result in longer term local control. The guidance as worded would not allow this for this select group of patients. In a similar regard there are a small subset of patients who refuse to have surgery in the form of an abdomino-perineal excision in view of the need for a permanent colostomy. Again these patients may be disadvantaged by the guidance as it reads as the Lyon 96-02 trial did achieve an increased rate of organ preservation for these patients with the addition of a contact brachytherapy boost. I would also strongly disagree that local excision in] locally advanced rectal patients who are unfit for surgery would be the better approach compared to external beam radiotherapy +/- brachytherapy boost.	
12	Consultee 2 NHS professional President, International Contact Radiotherapy Group Network	**1.1, 2.2**	In conclusion, the treatment approach for the vast majority of patients with locally advanced rectal cancer should be neo-adjuvant chemo/radiotherapy followed by radical surgery. However, there are caveats that not all patients are able to proceed down this route due to either co-morbidities precluding surgery or a refusal to have radical surgery. Selected patients in this group who have shown a response to external beam radiotherapy should be allowed the option of a contact brachytherapy boost to increase their chances of local control. As there are currently no clinical trials in this group, and the fact that the procedure is safe, it would be a disadvantage to these patients if the procedure was deemed to be only used in the context of research.	Thank you for your comments. IPAC considered your comments and amended 2.2 in the guidance. IPAC considered your comments but decided not to amend 1.1 in the guidance.
13	Consultee 1 NHS professional	**3.1 (overview efficacy - page 3)**	*a complete clinical response (no visible tumour; rectal mucosa clinically and endoscopically normal; or simple scar without suspicious induration) was reported in 26% (11/42) of patients in the CXB/EBRT group and 33% (12/36) of patients*	Thank you for your comments. This outcome was reported in study 1 (Ortholan 2012) in table 2 in the overview.

			in the EBRT-alone group at 5-week follow-up (no p value reported). Clinical Complete response (cCR) Highlighted in yellow- Data quoted is incorrect Actual published data •Four to 6 weeks after the end of EBRT, a complete CR was found in 11 patients in the experimental group, and in only one from the control group (P < .05). Explainer note- a complete clinical response in experimental group 26% (11/42) of patients in the CXB/EBRT group and 2.7% (1/36) of patients in the EBRT alone group. P value was reported in the original paper as (P <0.5). Therefore, no 'p' value reported is incorrect.	The error in this statement has been amended.
14	Consultee 1 NHS professional	**3.1 (overview efficacy - page 3, 13)**	***A complete clinical response was reported in 26% (11/42) of patients in the CXB+EBRT group and 33% (12/36) of patients in the EBRT-alone group at 5-week follow-up (no p value reported*** This statement is incorrect. A significant improvement was seen in favor of the contact x-ray boost for complete clinical response (24% v 2%) and for a complete or near-complete sterilization of the operative specimen (57% v 34%) The figure in the original paper Gerard, 2004 JCO) was Four to 6 weeks after the end of EBRT, a complete CR was found in 11 patients (11/45) in the experimental group (EBRT+ CXB), and in only one (1/ 43) from the control group(EBRT alone) (P <.05). Therefore, your statement is in correct.	Thank you for your comments. This outcome was reported in study 1 (Ortholan 2012) in table 2 in the overview. The error in this statement has been amended. The outcomes of this group of patients in the original paper Gerard 2004 are reported in Ortholan 2012 which is included in table 2 in the overview.
15	Consultee 1 NHS professional	**3.1 (overview efficacy - page 3)**	*In the same study, a clinical response (greater than 50% reduction in the product of 2 perpendicular parameters) was reported in 69%* A clinical response quote in actual paper was:-	Thank you for your comments. This outcome was reported in study 1 (Ortholan 2012) in table 2 in the

			A significant improvement was seen in favor of the contact x-ray boost for complete clinical response (24% v 2%) and for a complete or near-complete sterilization of the operative specimen (57% v 34%) Therefore , for both clinical (24 v 2%) and pathological response (57 v 34%) in favor of CXB boost was shown. This important data was incorrectly interpreted and quoted. This led to a bias in your conclusions.	overview. The error in this statement has been amended.
16	Consultee 1 NHS professional	**Page 5 overview**	***In a case series of 83 elderly patients with comorbidities and rectal cancer not suitable for, or refused, surgery and treated with CXB after radiotherapy (EBCRT/EBRT) for suspected residual disease (less than 3cm, cT2, cT3, more than 54% node positive) a complete clinical response (cCR; defined as complete absence of palpable, endoscopic or radiological evidence of residual tumour) was reported in 64% (53/83) of patients at a median follow-up of 2.5 years.*** These 83 patients (ref 2) were part of same cohort of 200 patients (ref 3). However, all the patients had EBCRT first followed by CXB boost within 4-6 weeks. Therefore, there is much more homogenous in the treatment they had received. In both groups cCR was sustained in 87% (46/53) [ref 2] and 86% (124/144)[ref 3].	Thank you for your comments. Text in study 2 and 3 in the overview has been amended to state that *'there may be considerable overlap in patient populations of study 2 and 3'.*
17	Consultee 1 NHS professional	**Page 4 overview**	***In a case series of 200 elderly patients with comorbidities and rectal cancer not suitable for, or refused, surgery and treated with combined CXB and EBCRT (n=183) or CXB alone (n=17), cCR was reported in 72% (144/200) of patients at a median follow-up of 2.7 years.*** Nearly half of these patients had locally advanced rectal cancer (cT3/cT4 45% and 37.5% cN1or 2). CXB boost was offered to responders with residual tumour <3cm as the patients were not suitable for surgery (majority) or refused it. cCR was sustained (organ preserved with no residual tumour) in 86% (124/144) of patients at 2.7 years follow up.	Thank you for your comments. **OPERA trial** (NCT02505750) has been added to the overview.

			Therefore, non-surgical treatment for locally advanced rectal cancer is not just for palliation. It does cure a high proportion of locally advanced rectal cancer. Phase 3 European randomised trial OPERA will be closing shortly and will report in 2023. This data when published will be important. You should at least mention this trial in your report.	
18	Consultee 1 NHS professional	**Page 4 overview**	**In the case series of 83 patients, tumour recurrence (local regrowth or distant relapse) after initial cCR was reported in 13% (7/53) of patients.** Tumour regrowth after EBCRT alone is much higher at 25-30% (Habr Gama, 2014; IWWD, 2018)	Thank you for your comments.
19	Consultee 1 NHS professional	**Page 6 overview**	**Disease-free survival (Kaplan–Meier estimates)** **In the RCT of 88 patients who had CXB and EBRT (n=45) or EBRT alone (n=43), disease-free survival rates were 53% and 54% respectively, at 10-year follow-up (p=0.99).** This trial was not powered to show survival difference as both groups had surgery after EBRT (with or without CXB boost).	Thank you for your comments. In this RCT, all patients had surgery (either sphincter-saving procedures or abdominoperineal resections) after initial treatment. The study assessed disease free survival and overall survival.
20	Consultee 1 NHS professional	**Page 7, 8 overview**	**Disease status** **In the case series of 83 patients, at a median follow-up of 2.5 years, 83% (69/83) of patients were free from cancer (this included 23 patients who had salvage treatment and 46 patients with sustained cCR).2 In the case series of 200 patients, at a median follow-up of 2.7 years, 81% (161/200) of patients were free from cancer (this included 23 patients who had salvage treatment and 46 patients with sustained cCR).3** These two data support the fact that locally advance rectal cancer can be cured without surgery.	Thank you for your comments.
21	Consultee 1 NHS professional	**Page 9 overview**	**Safety** **Death** **There were no deaths related to CXB in 3 case series of 83, 200 and 42 patients.1,2,3**	Thank you for your comments.

			Compare to surgery with surgical mortality ranging from 5-20% in this age group (above 70 years). This is remarkable. **Rectal ulceration- most of which healed within 3 to 6 months.2,3** **rectal necrosis- This healed within 3 to 6 months in all patients**	
22	Consultee 1 NHS professional	**Page 10 overview**	**Acute radiation proctitis (grade 3) after CXB and CRT was reported in 4% (1/27)** This was remarkable and acceptable low figure, yet in your conclusion stated severe short term toxicity which we do not observe.	Thank you for your comments. Safety is a key feature of the interventional procedure's programme. All safety issues are reported so patients can be informed and understand the risks and uncertainty about the frequency of complications in particular uncommon and serious ones.
23	Consultee 1 NHS professional	**Page 10 overview**	**Early grade 3 toxicities (including constipation, faecal incontinence, diarrhoea, and painful proctitis that was successfully treated) were reported in 9% (4/45)** These were remarkably low figures.	Thank you for your comments. Safety is a key feature of the interventional procedure's programme. All safety issues are reported so patients can be informed and understand the risks and uncertainty about the frequency of complications in particular uncommon and serious ones.
24	Consultee 1 NHS professional	**Page 10 overview**	**rectal perforation** We have never seen rectal perforation in any of the 2000 patients treated over 27 years at Clatterbridge.	Thank you for your comments. In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure,

				specialist advisers listed 'rectal perforation' as a theoretical adverse event.
25	Consultee 1 NHS professional	**1.2, page 10, 29 overview**	4. **Research** 4.1 Published evidence. There was no mention of the European multicentre randomised trial Lyon 96-02 which showed pathological evidence of efficacy for CXB when given addition to EBRT for T2 and T3 rectal tumours [8]. 4.2 Ongoing (ID: NCT02505750). There is an ongoing OPERA trial for patients with cT2 cT3 cN0 and cN1 tumour who are suitable for surgery. We have randomised 120 patients and trial is due to complete it accrual of 140 shortly. This trial should at least be mentioned in your recommendation as we are trying to establish an additional randomised trial evidence [9]. **References** 8. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the Lyon R96-02 randomized trial. J Clin Oncol 2004; 22: 2404–9. **https://doi.org/10.1200/JCO.2004.08.170** 9. European phase III study comparing a radiation dose escalation using 2 different approaches: External beam radiation therapy versus endocavitary radiation therapy with contact x-ray brachytherapy 50 kilovolts (kV) for patients with rectal adenocarcinoma. ID: NCT02505750. **https://www.clinicaltrials.gov/**	Thank you for your comments. The study by Gerard (2004) has been added to the appendix in the overview. The outcomes of this group of patients are reported in another paper (Ortholan, 2012) by the same author which is included in table 2. Details of the OPERA trial (NCT02505750) have been added to the overview.
26	Consultee 1 NHS professional	**Page 10, 29 overview**	**Trial registries** No mention of OPERA trial (Clinical Trials. gov, number NCT02505750) in your report.	Thank you for your comments. OPERA trial (NCT02505750) has been added to the overview.
27	Consultee 1 NHS professional	**Overview page 27**	***'No significant adverse events were reported in studies'.***	Thank you for your comments.

			Despite this statement, IP 1724 recommend that there was no evidence for safety of CXB. This statement is consistent with IPG532 on safety on CXB in early rectal cancer. The dose and fractionation of CXB given for advance rectal cancer is exactly the same as the dose and fractionation for early rectal cancer. there should not be any difference in toxicity. All 61 patients surveyed for IP1724 did not report any significant adverse events. This is our experience with over 2000 patients treated over 27 years at Clatterbridge.	IPAC considered your comments but decided not to amend 1.1 in the guidance. Whilst IPAC noted no significant adverse events had been reported in the studies, they considered the evidence on safety was inadequate in Q&Q and that this needed to be addressed with further research.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."