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REVIEW ARTICLE

Is There a Role for Primary Surgical Resection in the Palliative Rectal Cancer Setting: A Systematic Review

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ABSTRACT

Introduction: There are over 42,000 new cases of colorectal cancer diagnosed every year in the UK alone, a third of those being rectal in origin. Although there has been significant progress in the treatment of rectal cancer, overall, 5-year survival can still be as low as 17% for those with advanced disease. We aimed to assess the impact on of overall survival and quality of life of primary tumour resection in the palliative setting.

Method: A literature search was performed using Pubmed and Cochrane databases in March 2022. Bias was assessed using the Joanna Briggs institute checklist.

Results: Seven papers were included in the review; all retrospective cohort. A total of 809 patients underwent rectal resection in the presence of metastatic disease +/- adjuvant therapy. The median age was 61years, 59.7% male. 68.6% of patients presented with liver metastasis at the time of diagnosis. The most commonly reported symptoms preoperatively were bleeding and tenesmus. 4-50% of patients in each cohort underwent neoadjuvant therapy. Highest 30-day mortality reported was 7.3%. Both studies comparing resection v none demonstrated a higher overall survival for those undergoing surgery, with one showing 1year overall
survival 65v20%. Quality of life was not addressed across the literature.

Conclusion: Although there is some evidence to show a favourable overall survival for patients undergoing primary tumour resection in the palliative setting, this data is mainly old and across a heterogeneous population. A larger scale prospective study would be required to assess its potential role and impact upon quality of life.

Keywords: cancer, palliative, rectal

Introduction

There are over 42,000 new cases of colorectal cancer (CRC) diagnosed every year in the UK alone, with a third of those being rectal in origin[1]. Although there has been significant progress in terms of surgical technique through total mesorectal excision (TME)[2], magnetic resonance imaging (MRI) staging and the multidisciplinary approach overall 5-year survival can still be as low as 17%[3]. It is estimated that approximately 25% of patients will have hepatic metastases alone at the time of diagnosis[4], with 30% having metastatic disease at one or more sites[5]. Although the management of hepatic metastases has advanced with techniques such as radiofrequency ablation[6], surgical resection that would not achieve a R0 resection due to locally advanced disease or aggressive metastatic disease renders a patient into a palliative setting.

The World Health Organization (WHO) defines palliative care as an approach that improves the quality of life (QoL) of patients and their families facing the problems associated with life threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual[7]. The goal of any palliative intervention is to improve the QoL of the patient and / or their family.

Palliative treatment strategies for advanced rectal cancer are often tailored to symptoms, including the potential options of stenting, a defunctioning stoma, localised radiotherapy, laser or argon photocoagulation and depending on patient fitness and choice, chemotherapy[5]. Unlike colonic tumours, they are unable to be distally bypassed. The decision making for such patients is complex and a multidisciplinary team approach is needed for the choice of treatment based on the patients' symptoms, age, extent of disease and performance status. The gold standard treatment for locally advanced T4 rectal tumours is long-course chemoradiotherapy (LCRT) in an attempt to achieve clear surgical margins, followed by resection.[8] This, however, is associated with the high morbidity of pelvic dissection, impact on urinary and sexual function, anastomotic dehiscence and significant QoL factors, and so is often avoided in patients with palliative advanced metastatic disease.

Through the recent COVID-19 pandemic there was a significant reduction in patients actively seeking healthcare advice and therefore being referred for investigation and diagnosis[9]. This has resulted in a greater number of patients being diagnosed with advanced disease, and often presenting as an emergency, increasing the burden of patients proceeding down a palliative route. As a bridge to resection once the underlying COVID-19 knowledge base was built and green pathways were established, alternative oncological strategies were employed, particularly in the form of short-course radiotherapy[10,9]. Although the short-term evidence appeared safe, the long-term effects of this are yet to be fully established[11]. Over the past 15 years, there has also been a notable trend towards younger patients presenting with higher rates of distal tumours, particularly in the 20-29 years age range[12]. Both of these temporal changes raises the scenario of patients with a good performance status having a high physiological reserve to undergo pelvic surgery, even in the advanced metastatic disease palliative setting.

In this systematic review we aim to evaluate the current evidence for the role of palliative primary tumour resection and impact on overall survival.

Methods

A literature search was performed for full text articles using the PubMed, Cochrane databases. The search criteria string used was '(Rectal cancer OR rectal malignancy OR rectal carcinoma) AND (Palliative surgery OR palliative resection)' in March 2022.

Additional papers were detected by screening the references of relevant papers. Relevant titles were included in the search results, and those papers where then read through in full. The focus was limited to patients with rectal cancer however all study types were included in the search. Exclusion criteria included those reporting cancer elsewhere in the colonic tract alone, full article texts not available in English and articles prior to 1980.

Once the papers were identified, a search was performed to exclude duplicated results or duplicated data sets to produce a final list of papers. The review was registered on the PROSPERO database (CRD42022322631). A summary of the papers including is displayed in the PRISMA diagram in Figure 1. Bias was assessed using the Joanna Briggs Institute checklist (see appendix).

Results

A total of 7 papers were deemed eligible and included in the review. They were all retrospective cohort studies in nature, with an overall high risk of potential bias on scoring. In total 809 patients were included, all of whom underwent primary rectal

cancer resectional surgery in the palliative setting with or without adjuvant therapy. A summary of the studies included in the review are displayed in Table 1.

Table 1. *Summary of included studies*

Author	Year	Country	Journal	Study period	Total study size (n)
Al-Sanea *et al.* [13]	2003	Germany	ANZ journal of surgery	03/1990 to 02/ 1998	22
Heah *et al.* [14]	1997	Singapore	Disease of colon and rectum	06/ 1989 to 10/ 1995	54
Longo *et al.* [15]	1988	USA	Disease of colon and rectum	1980 to 1986	68
Verberne *et al.* [16]	2010	Netherlands	Colorectal disease	01/ 2002 to 12/ 2006	26
Nash *et al.* [17]	2002	USA	Annals of Surgical oncology	01/ 1991 to 12/ 2000	80
Kleespies *et al.* [18]	2009	Germany	International Journal colorectal disease	01/ 1996 to 12/ 2002	77
Sigurdsson *et al.* [19]	2007	Norway	Colorectal disease	01/ 1997 to 12/ 2001	482

Demographics

The median age at primary resection was 61 years, with a range of 54-64 years. The predominate gender was male comprising of 59.7% of the study population. The most commonly reported symptoms pre-operatively were bleeding per rectum and tenesmus, however other symptoms included a change in bowel habit, pelvic and abdominal pain, weight loss and anorexia. Twenty-one patients presented with obstructive symptoms. 68.8% of patients presented with liver metastasis at the time of diagnosis, with lung and peritoneum being the second two most common sites for metastasis.

Only 3 papers report the TN[20] staging of the primary tumour, which are demonstrated in Table 2. The most commonly reported tumour grade was T3 and nodal status N1 across those reported.

Table 2. *Table summarizing the tumour (T) and nodal (N) staging of tumours in patients with advanced rectal cancer*

	T2(%)	T3(%)	T4(%)	N0(%)	N1(%)	N2(%)
Nash *et al.* [17]	6	87	6	26	45	28
Kleespies *et al.* [18]	1	77	22	12	34	52
Sigurdsson *et al.* [19]	0	66	29	-	-	-

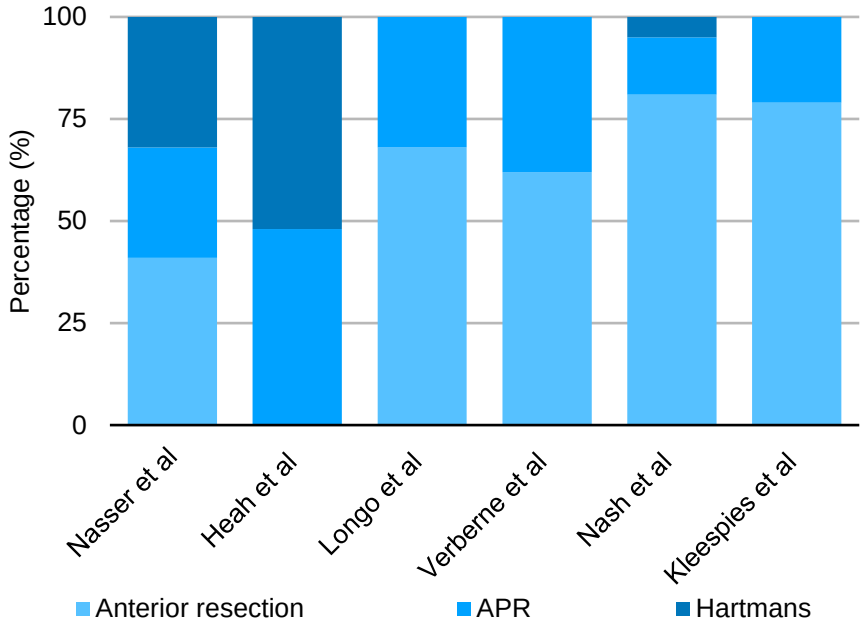
Neoadjuvant therapy

Across the studies, 4-50% of patients in each cohort underwent neoadjuvant therapy prior to their surgery. Al-Sanea *et al* [13] reported 11 patients receiving neoadjuvant therapy; 9 of those in the form of radiotherapy and 2 chemotherapy. Longo *et al*[15] included 3 (4.0%) patients receiving radiotherapy, and Nash *et al*[17] 4 (5.0%) patients receiving chemotherapy. Of interest the predominant neoadjuvant therapy that was reported was radiotherapy, with a smaller subset of patients receiving chemotherapy upfront.

Operative technique

Graph 1 demonstrates the various operative approaches that were employed for the resection of the primary tumour. Six out of the 7 papers reported the specific procedure employed. The most

common surgical approach was an anterior resection, consisting of 59.9% of all operations. An abdominoperineal resection (APR) accounted for 27.9% and lastly a Hartmans for 12.2% There were no pelvic exenterations performed.



Graph 1: *Surgical approaches for patients with advanced rectal cancer.*

Morbidity

Across the studies examined 15-54% of patients were reported to have had a post-operative complication, with a return to theatre rate of 5-14%.

Kleespies *et al* [18] reported that 54.5% of their patients developed post-operative complications. The most common being a superficial wound infection for 27.3% followed by anastomotic leak at 24.2%. Incisional hernia, post-operative bleeding and abscess formation accounted for 16.3%, 6.5% and 4.3% respectively. 14.3% required a return to theatre, with a median length of stay (LOS) of 15 days. Similarly, Heah *et al* [14] reported an overall complication rate of 40.7%, however with a short median LOS of 8 days.

Longo *et al*[15] identified pelvic sepsis as the highest post-operative complication, with an overall rate of 26.4%. Two patients required an emergency laparotomy, one for intra-abdominal sepsis for an anastomotic leak following stapled anastomosis for a low anterior resection, and the second for pelvic bleeding.
Nash *et al*[17] stated that 15.0% of their patient cohort developed complications. 5.0% underwent a return to theatre, for again either an anastomotic leak or pelvic bleeding. Other complications that were managed conservatively included 3 pelvic abscess that where drained percutaneously. The median LOS for this study was 9 days with 7 patients requiring readmission within 60 days.

Verberne *et al*[16] classified their 38.0% complications into either minor or major. Minor included urinary retention (n=3), urinary tract infections (n=1) and pulmonary infection (n=1). Major complications included respiratory insufficiency requiring ventilation (n=1), septic shock with multiorgan failure (n=1) and fascial dehiscence (n=1). The mean LOS in this study was 17 days, exceeded only by Al-Sanea *et al.* [13] at 18.6 days.

30-day Mortality

The highest 30-day mortality reported was Longo *et al* [15], at a rate of 7.3%. This was followed by Longo et al[15] at 6% , Kleespies *et al* [18] at 3.9% and Nash et al[17] at 1%. Advancing age, high ASA score, T4 stage of tumour and post-operative complications correlated with an increased 30-day mortality.

Adjuvant therapy

The use of adjuvant therapy was reported in all 8 papers. Al-Sanea *et al* [13] was the only cohort not to

report the use of chemotherapy, however 36.3% of patients received post-operative radiotherpy, four patients had radiotherapy for symptom control, two for bony metastasis, one for liver metastasis and one for peritoneal metastasis. Heah *et al* [14] report 50.0%, 7.4% and 20.3% of their patients receiving chemotherapy, radiotherapy and chemoradiotherapy respectively, they don't however specify the location of the adjuvant radiotherapy. Longo *et al* [15] report 66.1% of their patients receiving adjuvant therapy but don't provide a breakdown of the same or to the site provided. Verberne *et al* [16] and Nash *et al*[17] report 58.0% and 76.2% respectively of their patients received chemotherapy only. Nash *et al*[17] goes further to report that three patients received Hepatic arterial infusion chemotherapy and one received intraperitoneal chemotherapy. Kleespies et al[18] demonstrated that 66% of their patients received chemotherapy only and another 22.1% received a combination of chemoradiotherapy. Sigurdsson *et al* [19] was the study with the greatest population size and they report 43.9% of these patients receiving chemotherapy alone and 20.5% receiving radiotherapy. The site of radiation however hasn't been stated. As can be seen from the data the majority of patients received chemotherapy, which is in line with literature that supports the use of chemotherapy in the presence of advanced or metastatic disease. Radiotherapy is often used in the preoperative setting to help with symptom relief however it has no effect on the long-term survival of these patients.

Survival

Longo *et al* [15] reported 1-year survival of 65%. They observed no difference between survival of patients with advanced local invasion compared to patients with local metastases, however they did note a difference in patients with distant metastasis who survived significantly shorter periods of time compared to those with local invasion. Between their resected and non-resected group of patients with locally advanced disease they noted that patients who underwent resection survived significantly longer that the patients who were treated without resection, with 1-year overall survival (OS) 65% v 20% and 2-year OS 20% v 0%. The overall local recurrence rate reported was 6% with a median time of 20 months.

One-year survival across the Kleespies *et al* [18] cohort was 56.7%, with independent prognostic factors for reduced survival including a large tumour burden such as high pT stage, positive lymph nodes, positive local resectional margins, lack of postoperative tumour specific therapy and most significantly >50% hepatic parenchymal replacement. There was no association between OS and age, sex, symptoms, primary tumour site (colon or rectum), comorbidity of patients, metastatic spread (to more than one organ) or type of surgery (oncological vs segmental). Three-year survival was 5.9%. Al-Sena *et al* [13] reported 13.64% of patients surviving 3 years.

Verberne *et al* [16] also reported a significantly better OS for patients undergoing resection compared to those not. Resection of the primary tumour followed by chemotherapy led to a longer survival of patients that was independent of age, comorbidity and extent of disease. They report a 3.84% 3-year survival.

The highest 5-year survival was reported by Al-Sanea *et al* [13] at 5.0%, however with a note as to the lower mean age of their patients and lower morbidity and mortality rates. Kleespies *et al* [18] reported a 1.5% 5 year survival, with Longo *et al* [15] a rate of 0.0%.

Discussion

Although the data across the literature for patients undergoing primary rectal resection with a palliative intent is limited to only 7 papers, it is evident that the procedure is being carried out. Due to the nature of the disease, small cohorts and potential poor long-term outcomes, it is conceivable that there is under reporting of data that is desperately required to add to the field. The highest 30-day mortality reported was by Longo *et al* [15], at a rate of 7.3%, followed by Kleespies *et al* [18] at 3.9%, demonstrating that the procedure can be considered relatively safe in this high-risk cohort. Across the studies examined 15-54% of patients were reported to have had a post-operative complication, with a return to theatre rate of 5-14%. The most commonly reported complications included superficial wound infections and anastomotic leaks. Although conferring the benefits of the avoidance of stoma related morbidity, given the likelihood of these patients progressing to adjuvant chemotherapy and potential underlying limited physiological reserves the potential avoidance of an anastomosis, with careful counselling of the patient, may in fact be a safer option.

The most commonly reported pre-operative symptoms were rectal bleeding and tenesmus. Heah *et*

al[14] stated that patients reporting bleeding, tenesmus and diarrhoea symptoms were effectively eliminated in the post-operative period, however this was not the same across the board. Al-Sanea *et al*[13] also reports that the patients in their cohort also experienced minimal symptoms despite their progressive disease and they account a proportion of this to a well set up palliative community support post operatively. Longo et al[15] demonstrated that only 4% of their patients developed significant pelvic pain in the resected group compared to 14% in the non-resected group. They go on to comment that the overall QoL seemed better when palliative resection could be accomplished because of better control of pelvic disease, although no formal assessment was made. There is no formal assessment of QoL across our literature and therefore robust data in this regard is lacking and does not allow us to draw any conclusions within this paper.

Heah et al [14] looked at the difference between patients undergoing an APR and a Hartmann's procedure. They found that patients undergoing an APR had the main added complication of sepsis from the perineal wound. Half of patients reported wound infection and one third persistent post-operative perineal pain, highlighting the need for careful operative consideration and patient counselling. The type of operation performed could play an important part in the post operative recovery and associated morbidity. Contrary to this however the recent HiP study[21] done in 2020 demonstrated that there was no difference in the rate of complications between patients who underwent a Hartmans procedure vs intersphincteric APR. They demonstrated that serious perineal wound infections were lower than serious pelvic abscess and that the emotional wellbeing component of the FACT-C questionnaire was lower in patients who underwent the APR at 90 days compared to the other subgroup.

Longo *et al* [15] reported an overall 1-year survival of 65%, with patients who underwent resection surviving significantly longer than those without; 1-year OS 65% v 20% and 2-year OS 20% v 0%. Verberne *et al* [16] also reported a significantly better OS for those undergoing resection, with a 3.84% 3 year OS. They found that resection of the primary tumour followed by chemotherapy led to a longer survival of patients that was independent of age, comorbidity and extent of disease. The highest 5-year survival was reported by Al-Sanea *et al* [13] at 5.0%, although their cohort was noted to be at a younger age range and lower post-operative morbidity, again highlighting the importance of careful patient selection and intra-operative decision making. This data directly comparing the 2 oncological strategies is limited, although encouraging for reducing disease burden.

As a major limitation of our review, the most recent included paper was published in 2010. The management of rectal cancer, in terms of accurate disease staging, surgical approach and technique has progressed significantly during that time period and brought with it improved overall outcomes. There have been significant recent developments in the management of patients with rectal cancer. Operative techniques including laparoscopic and robotic approaches now dominate the field as they are hypothesized to provide better access to the pelvis, particularly in the obese male population[22]. In the palliative setting an early discharge and return to independence should be considered a key goal and minimally invasive techniques have been demonstrated to provide this.[23] With the introduction of the enhanced recovery after surgery (ERAS)[24] protocol we have also reduced length of hospital stay and post-operative complications. More up to date data is required to fully assess resections being performed with a palliative intent in the current setting to get a better idea of short and long-term outcomes. The most commonly resected tumour across the cohort was T3N1 disease, demonstrating a good intent to achieve clear surgical margins, but potentially under-representative of all suitable patients. The age range is also limited to 54-64 years, which may exclude patients who are potential candidates and introduce bias into morbidity rates. The ideal primary endpoint of any palliative study would be impact upon quality of life, however the lack of data within our literature prevents us from drawing any meaningful conclusions.

With a growing cohort of patients being diagnosed with both advanced disease and at a younger age changing the rectal cancer landscape, it is imperative that we build a more established evidence base for any oncological approach that may convey a safe means of improving overall survival and good QoL. Due to the nature of the disease, and level of heterogenicity, collecting large scale randomized data may be impossible. A multi-centre national prospective database may however be achievable with careful planning to help draw firmer conclusions from the data moving forward.

Conclusion

In conclusion, this systematic review has demonstrated that palliative resection for rectal cancer is indeed beneficial in a select group of patients. The

main benefits of offering this cohort of patients resectional surgery is to manage palliative symptoms and improve their quality of life. However, it is shown that patients who underwent surgery had a longer survival as compared to the cohort that didn't. One study reported that they were able to offer adjuvant chemotherapy thereby increasing their length of survival. With a relatively low 30 day mortality, palliative surgery is seen to be safe in this higher risk group of patients. More recent studies have shown no difference in the type of surgery offered to the patient. A limitation of this paper is that the most recent data is from 2010, since then there has been great developments in surgical techniques and enhanced post operative recovery. More recent data would be required to fully assess resections that have been done in a palliative setting and to formally address the impact of quality of life in this cohort of patients. We propose a multicentre national prospective database to achieve formal conclusions from the data in the future.

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