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A systematic review of outcomes after salvage abdominoperineal resection for persistent or recurrent anal squamous cell cancer

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ABSTRACT

AIM: Up to 30% of patients with squamous cell cancer of the anus (SCCA) will require a salvage abdominoperineal resection (APR) for either persistent or recurrent disease. The objective of this study is to assess cancer-related outcomes in patients with (i) persistent or (ii) recurrent SCCA.

METHOD: EMBASE and MEDLINE were searched. Publications were included if they assessed overall survival (OS), disease free survival (DFS), and locoregional recurrence or metastatic disease after salvage APR for persistent or recurrent SCCA.

RESULTS: A total of 28 retrospective, case series (study size ranged from 9 - 111) met our inclusion criteria. The median time to salvage APR was 2.6 months (IQR 2.6 – 5.0 months, 6 studies) for persistent disease and 27.6 months (IQR 15.0 – 32.7 months, 5 studies) for recurrent disease. The median five-year OS from the time of salvage APR was 45.0% (IQR 32.0 – 52.3%, 10 studies) for persistent disease and 51.0% (IQR 36.0-60.9%, 11 studies) for recurrent disease. The median 5 year DFS following salvage APR was 44.0% (IQR 29.5 – 53.0%, 10 studies) for all patients. Following salvage APR, median locoregional recurrence rate was 23.5% (IQR 15.8– 46.9%, 19 studies) and 9.0% (IQR 6.4 – 13.3%, 16 studies) of patients developed metastatic disease after salvage APR.

CONCLUSION: Our review characterizes the best evidence for outcomes following salvage APR for patients with persistent or recurrent SCCA. The evidence is limited by the quality of included studies, as many were single center case series.

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

This study is the first comprehensive review of long term outcomes following salvage APR after chemoradiation for SCCA. Although this type of cancer is rare, it is commonly seen by colorectal surgeons. We hope the information presented will allow a more informed discussion about surgery following failure of chemoradiation.

INTRODUCTION

Squamous cell carcinoma of the anus (SCCA) is a relatively rare cancer. The Surveillance, Epidemiology, and End Results (SEER) Program has estimated the lifetime risk of developing anal cancer as 0.2%. However, the incidence of SCCA has been increasing by an average of 2.2% each year over the last 10 years(1). Risk factors for development of SCCA include human papillomavirus (HPV) infection, cervical dysplasia or cancer, HIV infection, cigarette smoking, receptive anal intercourse, and immunosuppression(2).

Nigro demonstrated that upfront chemotherapy and radiation can lead to complete pathologic response for SCCA(3). This protocol has become the standard treatment for SCCA with a five year survival rate after successful treatment of approximately 80%(4). Guidelines recommend re-evaluation at 6-12 weeks after primary CRT to assess the response to chemoradiation therapy (CRT) (5).

Unfortunately, up to 30% of patients will fail treatment, with either persistent or locally recurrent disease(6). Persistent disease has been defined as biopsy-proven disease occurring between 3 to 6 months after completing CRT, while locally recurrent disease has been defined as disease occurring more than 6 months after the completion of CRT. Risk factors associated with persistent or recurrent SCCA include failure to complete CRT, higher disease stage, and HIV positive status(6, 7).

Locoregional treatment failures are usually managed with salvage abdominoperineal resection (APR), which is a morbid operation with a permanent colostomy and significant lifestyle implications. Due to the rarity of the condition, there is little evidence pertaining to the long term outcomes following salvage APR(8-10). Despite this, salvage APR continues to be the recommended treatment for persistent and locally recurrent disease(5, 11). To help guide clinicians and patients, a more thorough review of the literature is needed to allow for an informed discussion of the expected outcomes and complications and to help with prognostication.

The objective of this systematic review was to assess cancer-related outcomes in patients with either (i) persistent or (ii) locally recurrent SCCA who undergo salvage APR.

METHODS

We performed a systematic review to assess long-term outcomes following salvage APR in patients with persistent or recurrent SCCA. This systematic review is reported in accordance with the MOOSE guidelines(12). Recurrent SCCA in this context is defined as locally recurrent disease (i.e. intraluminal or regional).

INCLUSION CRITERIA

Studies were included if they assessed APR as a salvage procedure for SCCA after chemoradiation therapy. Full text articles between 1980-2018 were included regardless of the chemoradiation protocol provided initially. We elected to use this broad time range to ensure that all important and relevant studies were included in our review. Studies were included if they assessed at least one of the pre-specified outcomes.

OUTCOMES

Primary outcomes of interest included overall survival (OS), disease free survival (DFS), local-regional recurrence and metastatic disease. Secondary outcomes included wound complications and perioperative mortality. Although initially abstracted, complications were not ultimately reported due to the significant heterogeneity in the rates and which outcomes were reported.

SEARCH STRATEGY

The MEDLINE and EMBASE databases (1980–2016) was most recently searched on October 31, 2018. Two previous searches (October 5, 2016 and October 21, 2018) were previously completed. Search was limited to after 1980 as this was the period in which chemoradiation as definitive treatment for anal cancer was undertaken. A combination of medical subject headings (MeSH), key words and free text were used. The following terms were searched in EMBASE: (squamous cell carcinoma.mp. or exp squamous cell carcinoma/) AND (anal cancer.mp. or exp anus cancer/ OR exp anus disease/ or exp anus tumor/ or exp anus/ or exp anus carcinoma/ or exp anus surgery/ or exp anus cancer/) AND (exp recurrent disease/ or recurrence.mp. OR persistent.mp. OR exp salvage therapy/ or salvage surgery.mp. OR exp cancer recurrence/) AND (exp rectum abdominoperineal resection/ or abdominoperineal resection.mp.) MEDLINE was searched using the following terms: (exp Neoplasms, Squamous Cell/ OR exp Carcinoma, Squamous Cell/ OR squamous cell carcinoma.mp.) AND (exp Anal Canal/ or anal cancer.mp. OR exp Anus Neoplasms/) AND (persistent.mp. OR exp Salvage Therapy/ OR exp Neoplasm Recurrence, Local/ or recurrence.mp.) AND abdominoperineal resection.mp. The database search was performed with no language restrictions and no filters applied to study design.

We elected not to search the gray literature (e.g. conference abstracts and other unpublished works). We felt that including results from the gray literature was unlikely to change our conclusion.

STUDY SELECTION

All titles and abstracts identified by the literature search were reviewed independently and in duplicate by two authors (AS and GK). Articles deemed potentially eligible underwent full-text review by each author independently to determine if they met the above inclusion criteria. If disagreements in study selection occurred, consensus was obtained in consultation with a third author (SVP).

Data on study characteristics (year of publication, study design, location), patient characteristics (age, gender, HIV), stage of disease, chemoradiation protocol, follow-up period, and survival were obtained and recorded.. A standardized form was used to collect data from the included studies; this was again performed independently and in duplicate by AS and GK. Data collection sheets were compared for consistency. Differences were identified and resolved through discussion and consultation with the third author (SVP).

STATISTICAL ANALYSIS

Due to the expected limitations of study quality and comparability of studies, statistical analysis was limited to calculating weighted median results, and intra quartile ranges (IQR). Median survival (vs. mean survival) weighted for sample size was selected due to expected non-normal distribution of outcomes. Meta-analysis was not considered as we expected observational studies alone to be identified with high rates of heterogeneity.

RESULTS

Our literature search identified 608 citations. Titles and articles were screened to determine if they met inclusion criteria. Thirty-six articles were assessed at a full text level. Of these, 21 studies met our predefined eligibility criteria and were included in this systematic review (8-10, 13-30). The repeat search revealed an additional 28 citations and they were included in this review (31-35). The flow chart summarizing the systematic search strategy is included in Figure 1. Two additional studies were included after the free text search (36, 37). A total of 28 studies were included in the review. The flow chart summarizing the systematic search strategy is shown in Figure 1.

CHARACTERISTICS OF INCLUDED STUDIES

Table 1 summarizes the characteristics of the studies included. Data from the studies were accrued from 1980 to 2016. All studies were observational, case series studies. All study data was extracted from retrospective, chart reviews. There were no studies comparing outcome after APR for salvage (e.g. persistent or recurrent disease) with APR as primary therapy (e.g. contraindication to chemotherapy or radiation therapy).

The median number of patients in each study was 31.5 (range 9-111). Only one study contained data from multiple centres (51 patients from 6 centres) (16). The median age was 58.0 years (IQR 55.5 to 60.0). Age of patients was fairly consistent across studies. The median percentage of men was 28.0% (IQR 19.0 to 41.0%). HIV status was reported in 14 studies (9, 10, 15, 16, 19, 21, 22, 27-30, 33, 36); one study included only patients with HIV (15). Studies that included both HIV and non-HIV patients did not analyse the outcomes separately within these groups. The median percentage of patients with T3/T4 stage was 40.5% (IQR 35.0 – 62.6, 23 studies).

CHEMORADIATION THERAPY PROTOCOLS

Chemotherapy and radiation protocols were reported in 24 studies and are detailed in Table 2. There were two studies in which all patients received 5-FU with mitomycin C(18, 22) and one study in which all patients received 5-FU with cisplatin (19). Seventeen studies had patients who received a combination of 5-FU, mitomycin C, and cisplatin (8, 9, 13, 14, 16, 17, 20, 21, 23, 24, 27, 30-34, 37). Patients were treated primarily with bleomycin or carboplatin with 5-FU in one study (25). Other chemotherapy agents included cyclophosphamide(28) used in combination with 5-FU and/or MMC, but represented a small portion of patients. No rationale was provided with regard to selection of certain regimens. The median radiation dose was 50.4 Gy (IQR 45.6 – 56.0 Gy 25 studies).

SURVEILLANCE PROTOCOLS AFTER CRT

Surveillance protocols were described in ten studies(14, 15, 19, 23, 24, 26, 27, 32, 34, 35) and are detailed in Table 3. These studies started with clinical examination every two or three months for the first two to three years. The frequency was then extended up to six months until five years when it was extended to annual clinical examination. Routine imaging was performed in six studies (14, 15, 23, 24). Imaging was ordered if there was suspicion of locoregional or nodal recurrence in two studies (19, 27). Imaging was left to the discretion of the clinician in one study (34). Only one study reported using high resolution anoscopy for surveillance (15).

DEFINITION OF PERSISTENT VS. RECURRENT DISEASE

Twenty-five studies provided definitions of persistent versus recurrent disease (8-10, 13, 14, 16-29). Twenty-one studies (8-10, 13, 14, 16, 18-20, 23-26, 28, 29) used six months to differentiate persistent from recurrent disease. One study (10) separated recurrent disease into early (between 6 – 24 months) and late (after 24 months). The remaining four studies (17, 21, 22, 27) did not provide a time period to differentiate persistent from recurrent disease. Within these studies, persistent disease was defined as no response to treatment, whereas recurrent was defined as biopsy proven disease after an initial period of clinical response (i.e. no residual disease on physical exam, flexible sigmoidoscopy and/or imaging). Two papers studied only recurrent disease (22, 30). All studies used biopsies to prove recurrent disease. Two studies (21, 31) did not require biopsy for persistent disease due to concern of a false-negative result.

OUTCOMES AFTER SURGERY

Time to salvage APR was reported in eleven studies (9, 15, 20, 21, 23, 25, 28, 31) with the weighted median time to salvage APR 2.6 months (IQR 2.6 – 5.0 months, 6 studies) for persistent disease (15, 20, 21, 23, 28) and 27.6 months (IQR 15.0 – 32.7 months, 5 studies) for recurrent disease (20, 21, 23, 28).

For the studies that reported long-term outcomes, 19 studies (8, 13-15, 17, 18, 20-27, 29, 30, 33, 34) reported survival from the time of salvage APR with a weighted median follow-up time of 24.2 months (IQR 18.0 to 47.0). Five studies (9, 16, 19, 28, 31, 34, 35) reported survival from diagnosis of persistent or recurrent disease and not the surgical date; the weighted median follow-up time was 33.3 months (IQR 33.3 – 34.0). One study reported results from the time of neoadjuvant chemoradiation with a median follow-up time of 24 months (10).

The weighted median 5 year OS following salvage APR was 39.0% (IQR 27.3–52.0%, 14 studies) for all patients(13, 14, 17, 18, 20, 21, 23, 25-27, 29). The weighted median five-year OS from the time of salvage APR was 45.0% (IQR 32.0 – 52.3%, 10 studies) for persistent disease (8, 13, 17, 18, 21, 23, 25, 26) and 51.0% (IQR 36.0-60.9%, 11 studies) for recurrent disease (8, 13, 17, 18, 21-23, 25, 26).

For the studies that reported DFS, thirteen studies (8, 13, 14, 17, 20, 21, 23, 27, 29) reported survival from the time of salvage APR, while four studies (9, 16, 28) reported survival from diagnosis of persistent or recurrent disease and not the surgical date. The weighted median 5 year DFS following salvage APR was 44.0% (IQR 29.5 – 53.0%, 10 studies) for all patients (8, 13, 14, 17, 20, 21, 23, 27, 29). The study by Akbari(13) found that 5 year DFS was 58% for persistent disease while it was 36% for recurrent disease following APR. The study by Ghouti et al.(19) found that 5 year DFS from diagnosis of recurrent disease to be 31.1%, while the 5 year DFS from diagnosis of persistent disease was 48.2%.

Recurrences following salvage APR are summarized in Table 5. A weighted median of 23.5% (IQR 15.8– 46.9%, 19 studies) of patients developed locoregional recurrence (9, 13-21, 23-25, 27, 28, 30) and 9.0% (IQR 6.4 – 13.3%, 16 studies) of patients developed metastatic disease (9, 13-21, 23-25, 27-30) after salvage APR. More than one form of recurrence (locoregional, locoregional nodal, and metastatic disease) occurred in a weighted median of 7.4% of patients (IQR 3.6 – 25.0, 12 studies) (13, 14, 17, 20, 23-25, 27-30). Sites of distant metastases were reported in eight studies (15, 17, 20, 23, 24, 28, 29), which included liver, bone, lung, and brain. The most common site of metastases was liver. Chemotherapy was utilized for locoregional recurrences and metastatic disease. The chemotherapy regimen was not reported. Weighted median combined survival after recurrence following salvage APR was 19 months (IQR 11.0-23.0, 8 studies) (13, 17, 19, 23-25).

Meta-analysis comparing outcomes between those with persistent or recurrent disease was not attempted due to the significant variation in how the studies were reported. Studies typically assessed survival or disease free survival from date of surgery (not date of index diagnosis or start/completion of chemoradiation). As such, lead time bias exists in a way that was insurmountable. In addition, the nature of surveillance, definition of persistent vs. recurrence and reported outcomes (2 or 5 year survival vs. median survival) was inconsistent.

DISCUSSION

To our knowledge, this is the first systematic review that reports the long-term outcomes following salvage APR for persistent and recurrent squamous cell cancer of the anus. We found that five year overall survival was comparable for patients treated with persistent (45%) and recurrent disease (51%). After salvage APR, 24% of patients developed further recurrent disease and 9% of patients developed metastatic disease. Median survival among this group of patients was 19 months. Perioperative mortality was low within the assessed studies.

STRENGTHS AND LIMITATIONS

The primary strength of this review is in the comprehensive literature search and inclusive approach to identify studies for inclusion in this review. This study follows the reporting guidelines described by MOOSE(12). We reported a number of clinically important aspects of treatment and surveillance as well as a transparent assessment of the definitions used in the included studies for persistent vs. recurrent disease. This allows the reader to compare local practices to the published reports. The other strength of this study is in reporting clinically meaningful outcomes such as overall survival, disease free survival, local

recurrence and recurrent metastatic disease. These outcomes have only sparingly been reported in the past, and have never been included in any previous systematic reviews.

The limitations of this review relate to the methodologic and reporting quality of included studies. All studies are retrospective case series; only one of which was multi-center. There was inconsistency in how the definitions of persistent versus recurrent disease and outcomes were reported. In addition, it was unclear whether some patients were treated for persistent or recurrent disease in several studies. A number of studies reported survival from the time of salvage APR, while others reported survival from time of diagnosis of persistent/recurrent disease. We were able to calculate medians and intraquartile ranges only as the nature of the data reported did not lend itself to any form of sophisticated analysis. An additional limitation is that the stage of disease of treated patients was not consistently reported and could not be incorporated in our analyses. Clearly, more advanced stage disease at the time of resection would be associated with survival. Furthermore, the extent of surgery may have differed based on stage which would be associated with post operative complications.

Cancer outcomes also varied substantially between studies. We found overall survival to be as high as 65 – 70% at five years in some studies (19, 20), and as low as 21% at two years in another study(20). Due to the small size of included studies, and limitations in reporting, we were unable to explore the reasons for this variation.

The included studies also had significant clinical heterogeneity (if reported at all) in their surveillance protocols. This may have resulted in patients being misclassified into recurrent or persistent disease. Time to surgery from completion of chemoradiation was infrequently reported. This prevented an assessment of whether the definition of persistent vs. recurrent disease was used. Of some concern is that the median time to surgery for those

with persistent disease was only 2.6 months. Typically we would expect waiting up to six months to allow for the full effects of chemoradiation. This group may have had a complete response if given more time, or may have been progressing on treatment. Explanations within the included papers were not provided.

Due to the rarity of the use of salvage APR, many of the studies included patients over a broad time range. Changes in the utilization of imaging (i.e. MRI, PET), dosage of radiation treatment and selection of chemotherapy regimens may have occurred within these studies, which may affect outcomes over the study period. The inconsistent treatment of this disease over long periods of time is expected. Changes in how chemoradiation is delivered, surgical management, and assessment for local, regional and distant recurrence, result in heterogenous populations which make it difficult to analyze.

Finally, follow up duration varied substantially within studies. As such, our report on 5 year outcomes may have missed a number of patients who had shorter follow up duration. The summarized survival may be an overestimation.

MEANING OF THE STUDY

The results of this study provide the current best evidence for long term prognosis for those with recurrent or persistent squamous cell carcinoma of the anus. The study results will provide clinicians with summarized survival data. We have also reported the risks of metastatic disease or recurrent disease following salvage APR. This information will guide surgeons and patients in making an informed decision pertaining to surgery in this population.

Although we report a median time from chemoradiation to surgery for persistent disease as 2.6 months, we found that this detail was missing from a number of included studies. The five studies that included this detail (15, 20, 21, 23, 28) had overlapping

treatment periods, with all studies including patients from the 1990's and 2000's. If this duration does reflect the true findings, it would appear to be shorter than expected. As per the NCCN guidelines, assessment of chemoradiation response should be deferred until 8 – 12 weeks following completion. In the case of persistent disease, evaluation should be repeated in 4 weeks with treatment decisions to follow. Only in cases of progressive disease do the guidelines suggest early operation. The included studies did not differentiate between persistent and progressive disease. Perhaps a number of patients operated on within three months of completion of chemoradiation should have been re-evaluated and may have had further response to treatment.

Interestingly, we found that the median time to surgery for those with recurrent disease was 27.6 months. This again was based on a limited number of studies. This finding reflects the importance of continuing intensive follow up to identify those with later recurrence.

Most studies currently define persistent disease as biopsy proven disease within the first six months after chemoradiation therapy and recurrent disease as disease that occurs more than six months after treatment. However, the ACT II trial from the UK demonstrated increased clinical response to CRT with assessment at 26 weeks (78%) when compared to assessment at 11 weeks (52%) (38). This suggests that current studies assessing persistent disease may be including patients who would have had a complete clinical response if given the opportunity to do so.

CONCLUSION

Our review characterizes the best evidence for outcomes following salvage APR for patients with persistent or recurrent SCC. The quality of evidence is poor. It is limited by the quality of included studies, as many were single center case series with significant heterogeneity as there was no consistent definition of persistent versus recurrent disease. In addition, there was heterogeneity in the chemotherapy and radiation protocols. Further work, likely in the form of a population level study, is needed to study disease free survival outcomes and outcomes following secondary failure after salvage APR.

Table 1. Characteristics of published cases series of salvage APR following chemoradiation for persistent or recurrent squamous cell carcinoma of the anus.

Author (yr)	Type of Study	Recruitment time period	Sample Size (N)	Median Age (range)	% Male	% HIV	% T3/T4 Tumor Stage
Guerra (2018) (34)	Single centre, Case series (retrospective chart review)	1983-2015	41	60 (39 - 86)	44	5	63.4
Hagemans (2018) (37)	Single centre, Case series (retrospective chart review)	1990-2016	47	56 (48–66)	57.4	NR	40.5
Pedersen (2018) (36)	Single centre, Case series (retrospective chart review)	2011-2016	47	59 (43-82)	43	2	32.0
Pesi (2017) (32)	Single centre, Case series (retrospective chart review)	1988-2012	20	60 (36–76)	45	NR	70.0
Alamri (2016) (31)	Single centre, Case series (retrospective chart review)	1998-2014	27	66 (42-84)	37	NR	NR
Hannes (2016) (22)	Single centre, Case series (retrospective chart review)	2003-2013	14	51 (42-75)	64	36	14.3
Hardt (2016) (33)	Single centre, Case series (retrospective chart review)	2008-2014	17	56 (36–74)	59	0	NR
Severino (2016)(10)	Single centre, Case series (retrospective	1992-2012	36	PD: 66 (56.5-72) Early RD: 56 (48-	39	17	55.6

	chart review)			63) Late RD: 56.5 (46.5-75.2) 52 (41-70)			
Cunin (2014)(15)	Single centre, Case series (retrospective chart review)	1989-2012	9		100	100	55.6
Hallemeier (2014) (21)	Single centre, Case series (retrospective chart review)	1993-2012	32	53 (34-87)	19	0	37.5
Correa (2013) (14)	Single centre, Case series (retrospective chart review)	1982-2011	111	58 (31-85)	16	NR	69.4
Harris (2013) (35)	Single centre, Case series (retrospective chart review)	1997-2010	11	NR (looked at all patients who chemorads)	NR (looked at all patients who chemorads)	NR (looked at all patients who chemor ads)	NR
Lefevre (2012) (9)	Single centre, Case series (retrospective chart review)	1996-2009	105	55.5 (30.3–86.1)	27	11	NR
Eeson (2011) (16)	Multi-centre, Case series (retrospective chart review, patient registry)	1998-2006	51	60* (35-88)	33	12	55.0
Wright (2011) (30)	Single centre, Case series (retrospective chart review)	1992-2007	14	45 (35 - 74)	7	7	29.0
Goere (2009) (20)	Single centre, Case series (retrospective chart review)	1990-2006	18	52.5 (37-74)	28	NR	38.9

Mariani (2008) (23)	Single centre, Case series (retrospective chart review)	1969-2003	83	61 (35-91)	11	NR	34.9
Mullen (2007) (24)	Single centre, Case series (retrospective chart review)	1990-2002	31	49 (31–75)	19	NR	41.9
Schiller (2007) (27)	Single centre, Case series (retrospective chart review)	1987-2006	40	57 (35 - 85)	28	18	35.0
Stewart (2007) (28)	Single centre, Case series (retrospective chart review)	1985-2001	22	60.5 (42 - 87)	41	0	56.8
Papaconstantinou (2006) (8)	Single centre, Case series (retrospective chart review)	1992-2002	15	55.4* (35.2 - 77.2)	47	NR	26.4
Ferenschild (2005) (18)	Single centre, Case series (retrospective chart review)	1985-2000	18	59* (41-83)	50	NR	28
Ghouti (2005) (19)	Single centre, Case series (retrospective chart review)	1987-2002	36	57.9 (32-82)	56	8	58.3
Akbari (2004) (13)	Single centre, Case series. (retrospective chart review)	1980-2001	62	58 (32-83)	34	NR	35.5
Nilsson (2002) (25)	Single centre, Case series (retrospective chart review)	1985-2000	35	72 (39-89)	26	NR	37.1
van der Wal (2001) (29)	Single centre, Case series (retrospective chart review)	1980-1998	17	54* (34 – 73)	47	6	NR
Pocard (1998) (26)	Single centre, Case series (retrospective	1986-1995	21	65* (40 -84)	29	NR	62.6

	chart review)						
Ellenhorn (1994) (17)	Single centre, Case series (retrospective chart review)	1980-1992	38	55 (no range reported)	42	NR	65.8

NR = Not reported

*mean was reported for these studies

Table 2. Chemotherapy, radiation, and surveillance protocols for published cases series of salvage APR following chemoradiation for persistent or recurrent squamous cell carcinoma of the anus.

Author (yr)	Chemotherapy	Radiation Dose	History Physical Exam Frequency	Anoscopy/Flexible Sigmoidoscopy Frequency	Imaging Frequency	Definition of Persistent (PD) vs. Recurrent Disease (RD)
Guerra (2018) (34)	5-FU + MMC (90%)	56 Gy	Q3 mos for the first 3 yr, q6 mos out to 5 yrs and annually thereafter	NR	At the clinician's discretion	PD: incomplete response to primary treatment. RD: tumor relapse > 6 months following primary therapy and after an initial complete response.
Hagemans (2018) (37)	5-FU + MMC (76.6%) 5-FU only (2.1%) No chemotherapy	60 Gy	NR	NR	NR	PD: histologically proven anal SCC < 6 months. RD: biopsy-proven recurrent anal SCC > 6 months.

	(21.3%)					
Pedersen (2018) (36)	NR	NR	NR	NR	NR	NR
Pesi (2017) (32)	5-FU (15%); 5-FU + MMC (80%) Unknown (5%)	55 Gy	Q6 mos for 2 yrs	NR	CXR, and MRI or CT scan annually. PET scans were used for suspected recurrence.	PD: histologically proven epidermoid carcinoma < 6 mos after CRT. RD: histologically proved epidermoid carcinoma > 6 mos
Alamri (2016) (31)	5-FU + MMC (66.7%) 5-FU (3.7%) 5-FU + cisplatin (3.7%)	42.5 Gy (36-55.8)	NR	NR	NR	PD: incomplete clinical response to the primary treatment. *Biopsy confirmation was not necessary due to risk of false negative (confirmed on final pathology) RD: tumour regrowth after an initial complete pathological response (>6 months)
Hannes (2016) (22)	5-FU + MMC (100%)	50.4 Gy + 9.7 Gy	NR	NR	NR	RD: biopsy proven result in the follow-up period.
Hardt (2016) (33)	MMC+5-FU (53%) MMC+5-FU+ cisplatin (29%) RT + 5-FU (6%) None (12%)	54 Gy (50.4–59.4 Gy)	NR	NR	NR	PD: biopsy proven result less than 6 mos after CRT. RD: biopsy proven result 6 mos or more after CRT
Severino	NR	NR	NR	NR	NR	PD: disease appear less

(2016)(10)						than 6 months after CRT. RD: disease appearing after 6 months (early within 24 months; late after 24 months).
Cunin (2014)(15)	NR	NR	Q3 months for the first 3 years then annually.	High resolution anoscopy Q1 year	CT Abdo/Pelvis q1 year (after 1996)	NR.
Hallemeier (2014) (21)	5-FU +MMC (67%) 5-FU+Cisplatin (16%) 5-FU+MMC+ci splatin (6%) 5-FU alone (3%)	54 Gy (range, 40.8–63)	NR	NR	NR	PD: incomplete clinical response to primary CRT. Biopsy confirmation was not required due to risk of false negative. RD: initial clinical response to primary CRT with subsequent clinical evidence of tumor regrowth.
Correa (2013) (14)	5-FU + MMC (73%) or cisplatin (27%).	41.4 to 45 Gy with 10 Gy boost.	Q3 months in the first 2 years; q6 months from years 3 -5.	NR	CXR + U/S of abdomen & pelvis q6 months. Then CT, EUS, MRI in the 1990's.	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result more than 6 mos after initial clinical response.
Harris (2013) (35)	5-FU+MMC 5-FU + cisplatin 5-FU alone Other/not recorded*	50.40 Gy	q2 mos for 2 yrs and then q 6 mos up to 5 years	NR	CT scan at 12 and 24 months	PD: biopsy-confirmed cancer < 6 mos following completion of chemoradiotherapy. RD: biopsy-confirmed cancer > 6 mos

Lefevre (2012) (9)	5-FU (91%) and/or Cisplatin (83%)	60-64 Gy. Assessment done at 40 Gy	NR	NR	NR	PD: persistent ulceration or re-emergence of lesion within 6 months of primary CRT. RD: lesions appearing after 6 months of primary CRT. *unclear if biopsy confirmation was necessary.
Eeson (2011) (16)	5-FU + MMC or cisplatin. "Vast majority received MMC. Small minority received cisplatin"	50 Gy + 10 - 15 Gy boost.	NR	NR	NR	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result more than 6 mos after initial clinical response.
Wright (2011) (30)	5-FU+MMC (50%) 5-FU+MMC+Cisplatin (21.5%) 5-FU+Cisplatin (7%) Other (21.5%)	4500 cGy (4500 – 6000 cGy)	NR	NR	NR	NR
Goere (2009) (20)	5-FU + MMC (30%)	45 Gy.	NR	NR	NR	PD: biopsy proven result less than 6 mos after

	5-FU + cisplatin. (70%)					primary CRT. RD: biopsy proven result more than 6 mos after initial clinical response.
Mariani (2008) (23)	5-FU + MMC or cisplatin (did not differentiate).	50 Gy + 15-20 Gy	q 3-6 months.	NR	CXR + liver U/S prior to 1990 CT A/P after 1990.	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result 6 mos or more after initial clinical response.
Mullen (2007) (24)	5-FU + Cisplatin (55%) 5-FU+Mitomycin C (33%) 5-FU only (3%) Unknown (3%)	55 Gy	Q3-6 months	NR	CXR + CT A/P q1 yr	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result 6 mos or more after initial clinical response.
Schiller (2007) (27)	5-FU+MMC (89%) 5-FU+MMC+Cisplatin (8%) 5-FU+Cisplatin (3%)	5,400 cGY	Patients were examined by rad onc q2 mos for the first 2 years, every 6 mos for the next 3 years, and thereafter annually.	NR	Imaging was obtained only if there was a suspicion of persistent or recurrent disease on clinical exam.	PD: Patients who never achieved a documented complete clinical response RD: disease arising after a complete clinical response. *clinical response based on radiation oncologist documenting no evidence of residual disease for at least 1 month at some point after completing CRT.

Stewart (2007) (28)	5-FU (95%) MMC (73%) Cyclophosphamide (9%)	47 Gy (50-60 Gy)	NR	NR	NR	PD: disease appear less than 6 months after CRT. RD: disease appearance 6 months after CRT.
Papaconstantinou (2006) (8)	5-FU + MMC (84%) 5-FU+cisplatin. (16%)	5208 cGy (4500-6125)	NR	NR	NR	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result 6 mos or more after initial clinical response.
Ferenschild (2005) (18)	5-FU + MMC (100%).	60 Gy. (40 – 80 Gy)	NR	NR	NR	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result after a period of initial clinical response.
Ghouti (2005) (19)	5-FU + cisplatin.(100 %)	45 Gy.	q3 months x 2 years, q6 months for year 3-5, and then annually	NR	Completed if there was suspicion of inguinal or pelvic recurrences.	PD: biopsy proven result immediately after primary CRT. RD: biopsy proven result more than 6 months.
Akbari (2004) (13)	5-FU + MMC or cisplatin. (did not differentiate)	3,000 - 6,120 cGy	NR	NR	NR	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result more than 6 mos after initial clinical response.
Nilsson (2002) (25)	Bleomycin (41%) 5-FU+ carboplatin (50%)	60 Gy	NR	NR	NR	PD: biopsy proven result less than 6 mos after primary CRT. RD: biopsy proven result 6 mos or more after initial

	5-FU+cisplatin (3%).					clinical response.
van der Wal (2001) (29)	5-FU+MMC (76%) 5-FU (6%) 5-FU+Cisplatin (12%) 5-FU+MMC+L V (6%)	5275 cGy (3400 to 6000 cGy)	NR	NR	NR	PD: biopsy proven result within 6 mos of completing CRT. RD: biopsy proven result more than 6 mos after a normal post-treatment biopsy.
Pocard (1998) (26)	NR	5,400 cGy (4,000 – 6,500 cGy)	Clinical evaluation q 2 mos during the first year, then q4 mos in second yr, q6 mos until end of yr 5 and then annually	NR	NR	PD: biopsy proven result less than 6 mos after CRT. RD: biopsy proven result 6 mos or more after CRT.
Ellenhorn (1994) (17)	5-FU + MMC (92%) 5-FU alone (8%)	3,000 – 6,500 cGy.	NR	NR	NR	PD: biopsy proven result > 1 month after CRT. RD: biopsy proven result after a period of initial clinical response.

NR = Not reported

*Study did identify what type of chemo/rads patients who underwent salvage surgery had.

Table 3. Indications and mean time to surgery in published case series of salvage APR following chemoradiation for persistent or recurrent squamous cell carcinoma of the anus.

Author (yr)	Patients Who Completed CRT (%)			Median Time to APR (mos)			Indication for Surgery	
	Combined	Persistent	Recurrent	Combined	Persistent	Recurrent	Persistent Disease (%)	Recurrent Disease (%)
Guerra (2018) (34)	78	NR	NR	NR	NR	NR	46.3	53.7
Hagemans (2018) (37)	78.7	NR	NR	NR	5	15	48.9	51.1
Pedersen (2018) (36)	60	NR	NR	9.1	NR	NR	NR	NR
Pesi (2017) (32)	100	100	100	NR	NR	NR	75	25
Alamri (2016) (31)	74.1	NR	NR	15	NR	NR	48.0	52.0
Hannes (2016) (22)	100	N/A	100	NR	NR	NR	0.0	100.0
Hardt (2016) (33)	89	NR	NR	NR	NR	NR	47.1	35.3
Severino (2016)(10)	NR	NR	NR	10	NR	NR	30.6	69.4
Cunin (2014)(15)	100	100	100	8	8	NR	88.9	11.1
Hallemeier (2014) (21)	94	NR	NR	NR	2	27.6	28.1	71.9

Correa (2013) (14)	80.2	NR	NR	NR	NR	NR	55.0	45.0
Harris (2013) (35)	100	100	100	NR	NR	NR	54.5	45.5
Lefevre (2012) (9)	73.3	NR	NR	15.3	NR	NR	40.0	52.4
Eeson (2011) (16)	96	NR	NR	NR	NR	NR	39.2	60.8
Wright (2011) (30)	92.9	N/A	92.9	NR	NR	NR	0.0	100.0
Goere (2009) (20)	55.6	NR	NR	NR	4	23.5	38.9	44.4
Mariani (2008) (23)	14.5	17.1	11.9	6.5	2.6	32.7	49.4	50.6
Mullen (2007) (24)	100	100	100	NR	NR	NR	35.5	64.5
Schiller (2007) (27)	95	NR	NR	NR	NR	NR	47.5	52.5
Stewart (2007) (28)	100	100	100	NR	3.0	15.0	40.9	59.1
Papaconstantinou (2006) (8)	100	100	100	NR	NR	NR	46.7	53.3
Ferenschild (2005) (18)	100	100	100	NR	NR	NR	38.9	61.1
Ghouti (2005) (19)	72.2	80	66.7	NR	NR	NR	41.7	58.3
Akbari (2004) (13)	100	100	100	NR	NR	NR	46.8	53.2
Nilsson (2002) (25)	65.7	71.4	57.1	5.8	NR	NR	60.0	40.0
van der Wal (2001) (29)	100	100	100	NR	NR	NR	70.6	29.4

Pocard (1998) (26)	14.3	NR	NR	NR	NR	NR	52.4	47.6
Ellenhorn (1994) (17)	100	100	100	NR	NR	NR	63.2	36.8

NR = Not reported

Table 4. Perioperative mortality and survival data in published cases series of salvage APR following chemoradiation for persistent or recurrent squamous cell carcinoma of the anus

Author	Periopera tive Mortality (%)	Median Follow- up (mos)	Definitio n of start of follow up	Overall Survival			Disease Free Survival		
				Combined	Persistent	Recurrent	Combined	Persistent	Recurrent
Guerra (2018) (34)	0	20	Diagnosi s of recurrent /persiste nt disease	51% at 5 yrs	NR	NR	47% at 5 yr	NR	NR
Hagemans (2018) (37)	0	80	Time of surgery	41.6% at 5 yrs	40.4% at 5 yrs	41.7% at 5 yrs	51.1 at 5 yrs	NR	NR

Pedersen (2018) (36)	4	20	Time of surgery	39 mos	NR	NR	32 mos	NR	NR
Pesi (2017) (32)	0	NR	Time of surgery	75% at 1 yr, 60% at 3 yrs, and 37.4% at 5 yrs	73.3% at 1 yr, 60% at 3 yrs, and 32% at 5 yrs.	80% at 1 yr, 60% at 3 yrs, and 60% at 5 yrs.	67% at 1 yr, 53 at 3 yrs, and 35% at 5 yrs	NR	NR
Alamri (2016) (31)	0	NR	Diagnosis of recurrent /persistent disease	78% at 5 yrs	NR	NR	NR	NR	NR
Hannes (2016) (22)	NR	62	Time of salvage surgery	N/a	N/a	86% at 5 yr	NR	N/A	NR
Hardt (2016) (33)	NR	27.3	Time of salvage surgery	33.4 mos	NR	NR	NR	NR	NR
Severino (2016) (10)	NR	24	Neoadjuvant chemoradiation	46% at 3 yr	31.8% at 2 yr	62.3% at 2 yr	NR	NR	NR
Cunin (2014) (15)	0	12	Time of salvage surgery	25% at 2 yrs	NR	NR	NR	NR	NR
Hallemeier (2014) (21)	0	19.2	Time of salvage surgery	23% at 5 yr, 17% at 10 yr	45% at 5 yr	14% at 5 yr	47% at 1 yr, 17% at 5 yr, 17% at 10 yr	NR	NR

Correa (2013) (14)	0	16	Time of salvage surgery	60% at 2 yrs, 24.5% at 5 yrs	NR	NR	29.5% at 5 yr	NR	NR
Harris (2013) (35)	0	NR	Time of salvage surgery	NR	NR	NR	64% at 5 yrs	NR	NR
Lefevre (2012) (9)	2.1	33.3	Diagnosis of recurrent/persistent disease	61% at 5 yr	NR	NR	48% at 5 yr	NR	NR
Eeson (2011) (16)	2	34	Diagnosis of recurrence.	29% at 5 yr	NR	NR	24.7% at 5 yr	NR	NR
Wright (2011) (30)	NR	17	Time of salvage surgery	21.4% at 2 yr	N/a	21.4% at 2yr	NR	N/A	NR
Goere (2009) (20)	5.6	33	Time of salvage surgery	67% at 5 yr	NR	NR	53% at 5 yr	NR	NR
Mariani (2008) (23)	4.8	104	Time of salvage surgery	56.5% at 5 yr	52.3% at 5 yr	60.9% at 5 yr	75.5% at 5 yr	NR	NR
Mullen (2007) (24)	0	29	Time of salvage surgery	64% at 5 yr	NR	NR	NR	NR	NR
Schiller (2007) (27)	5	18	Time of salvage surgery	53% at 3 yr, 39% at 5 yr	NR	NR	35% at 3 yr, 30% at 5 yr	NR	NR

Stewart (2007) (28)	0	15	Diagnosis of recurrent/persistent disease	18 months (median)	17.5 months (median)	18.5 months (median)	10.5 months (median)	8.5 months (median)	11.5 months (median)
Papaconstantinou (2006) (8)	NR	14.4	Time of salvage surgery	40% at median follow-up of 14.4 months	34% at 2 yr, 0% at 5 yr	75% at 2 yr, 28% at 5 yr	47% at median follow-up of 14.4 months	NR	NR
Ferenschild (2005) (18)	0	16	Time of salvage surgery	30% at 5 yr	63% at 5 yr	13% at 5 yr	NR	NR	NR
Ghouti (2005) (19)	0	67	Diagnosis of recurrence/persistent disease.	69.4% at 5 yr	60.7% at 5 yr	71.5% at 5 yr	NR	31.1% at 5 yr	48.2% at 5yr
Akbari (2004) (13)	1.6	24.2	Time of salvage surgery	33% at 5 yr	31% at 5 yr	51% at 5 yr	NR	36% at 5 yr	58% at 5 yr
Nilsson (2002) (25)	0	33	Time of salvage surgery	52% at 5 yr	33% at 5 yr	82% at 5 yr	NR	NR	NR
van der Wal (2001) (29)	0	53	Time of salvage surgery	47% at 5 yr	NR	NR	44% at 5yr	NR	NR

Pocard (1998) (26)	0	40	Time of salvage surgery	58% at 3 yr, 33% at 5 yr	71.6% at 3 yr, 59.7% at 5 yr	29% at 3 yr, 0% at 5 yr	NR	NR	NR
Ellenhorn (1994) (17)	0	47	Time of salvage surgery	44% at 5 yr	47% at 5 yr	36% at 5 yr	44% at 5 yr	40 months (median)	20 months (median)

* Low number of studies reporting DFS separating persistent and recurrent disease

Table 5. Recurrence data after surgery in published case series of salvage APR following chemoradiation for persistent or recurrent squamous cell carcinoma of the anus

Author (yr)	Median time to recurrence (months)	Recurrence after Salvage APR				Sites of distant metastases (n)	Management of Recurrence		Survival
		Nodal (n)	Local (n)	Metastatic (n)	Combination		Chemotherapy/Radiation (n)	Surgery	
Guerra (2018) (34)	NR	2.4% (1)	19.5% (8)	9.7% (4)	14.6% (6)	NR	Radiation Therapy: 3 Chemotherapy: 6 CRT/Exenteration: 2	Partial hepatectomy (1); Inguinal lymphadenectomy (1)	NR

Hagemans (2018) (37)	NR	4.3% (2)	6.4% (3)	6.4% (3)	29.5% (13)	Liver, adrenal gland, peritoneum	Radiation Therapy: 2 Chemother	Nodal dissection: 8	12 mos
Pedersen (2018) (36)	NR	NR	NR	NR	NR	NR	NR	NR	8 mos
Pesi (2017) (32)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alamri (2016) (31)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hannes (2016) (22)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hardt (2016) (33)	NR	17.6% (3)	23.5% (4)	NR	NR	NR	NR	NR	NR
Severino (2016)(10)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cunin (2014)(15)	NR	11.1% (1)	11.1% (1)	11.1% (1)	NR	Bone & Lung (1)	NR	NR	NR
Hallemeier (2014) (21)	Locoregional 0.6 yrs (0.2–3.7) Distant 0.8 yrs (0.1–2.8)	NR	46.9 % (15)	31.3 % (10)	NR	NR	NR	NR	Overall 5 yr = 47% Locoregional 5 yr = 51% Distant mets 5 yr = 40%
Correa (2013) (14)	NR	NR	47.7% (53)	9.0% (10)	7.4% (5) [L+M]	NR	NR	NR	NR
Harris (2013) (35)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lefevre	NR	11.4%	16.2%	13.3%	NR	NR	NR	NR	NR

(2012) (9)		(12)	(17)	(14)					
Eeson (2011) (16)	NR	NR	51.0% (26)	11.8% (6)	NR	NR	NR	NR	NR
Wright (2011) (30)	8 mos (3-18)	NR	28.6% (4)	NR	50% (7); 3 = local + nodes 4 = local + mets	NR	NR	NR	NR (not separated from those who did not have recurrence)
Goere (2009) (20)	20.8 (2-32) mos	NR	5.5% (1)	16.6% (3)	16.6% (3) 1 = local + nodes 2 = local + mets	Lung (4) & Liver (1)	100% chemotherapy	NR	NR
Mariani (2008) (23)	NR	4.8% (4)	7.2% (6)	4.8% (4)	3.6% (3) [L+M]	Mets only: Bone (1) + Liver (3)	Locoregional : 7 = no therapy 1 = chemotherapy 1 = brachytherapy Nodal: 1 = chemotherapy	3 (LND)	Median survival after APR recurrence: 23 mos Mean survival: Locoregional: 11 mos [1-33] Nodal: 12 mos [1-23]
Mullen (2007)	NR	12.9%	29.0%	9.8% (3)	12.9% (4)	Liver	1 nodal = Lymph Node		Median

(24)		(4)	(9)			(4), Lung + Brain (1), Lung (1)	Dissection+ cisplatin		survival: 33 months
Schiller (2007) (27)	4.3 mos (2-37)	NR	20% (8)	7.5% (3)	25% (10)	NR	Supportive treatment: 10% (2) Palliative surgery: 19% (4) Chemotherapy: 19% (4) Radiation only: 19% (4) Chemotherapy: 29% (6) Surgery + chemo: 5% (1)		NR
Stewart (2007) (28)	9 mos (2-50) RD: 11.5 (8 -50) PD: 5 (2-10)	NR	31.8% (7)	4.5% (1)	13.6% (3)	Liver (2) Bone (2)	NR	NR	NR
Papaconstantinou (2006) (8)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ferenschild (2005) (18)	NR	38.9% (7)	11.1% (2)	38.9% (7)	NR	NR	(Nodal recurrence) Chemotherapy: 3; Radiotherapy with hyperthermia :3	(Nodal recurrence) 1	NR
Ghouti (2005) (19)	Mean time: 30 mos	19.4% (7)	47.4% (9)	19.4% (7)	NR	NR	16 Palliative chemotherapy for locoregional	7 (Nodal recurrence; treated with	Mean survival for metastase

							& metastases	salvage LND)	s: 11 mos
Akbari (2004) (13)	9.4 (1.4–57.9)	NR	24.2 % (15)	6.5% (4)	3.2% (2) [L+M]	NR	45.5% (10)	54.5%(12)	2 yr RFS = 65% 5 yr RFS = 46% Median survival = 57.9 mos
Nilsson (2002) (25)	NR	NR	34.3% (12)	2.9% (1)	5.8% (2)	NR	NR	NR	Median survival: 19 mos [1-33]
van der Wal (2001) (29)	NR	29.4% (5) local or nodal		17.6% (3) (local + mets)			Supportive therapy: 50% (4) Chemotherapy: 50% (4)		NR
Pocard (1998) (26)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ellenhorn (1994) (17)	NR	13.2 % (5)	15.8% (6)	NR	31.6% (12) local + mets	Liver (9) & Lung (6)	NR	NR	Median survival = 11 mos

NR = Not Reported

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Figure 1. Flowchart summarizing systematic search strategy.