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Review Article

# State of the art treatment for stage I to III anal squamous cell carcinoma: A systematic review and meta-analysis

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ABSTRACT

*Background and purpose:* This systematic review summarised and critically appraised evidence on the efficacy and safety of interventions for anal cancer to support the panel of experts developing the national evidence-based anal cancer guideline in Germany.

*Materials and methods:* We conducted a systematic review and meta-analyses of interventions for the treatment of stage I to III anal squamous cell carcinoma (SCCA). We systematically searched several databases and included any randomised controlled trial (RCT) assessing the pre-specified patient populations, regardless of the interventions studied. Non-randomised controlled studies of selected, pre-specified interventions were included if RCTs were not available or contained insufficient information. Where possible, we conducted meta-analyses and critically assessed confidence in the effect estimates using the GRADE approach.

*Results:* Our searches yielded 10,325 (25 October 2018) and 889 hits (update search on 18 July 2019). Among the 41 studies (47 publications) included, we identified 19 comparisons of interventions for SCCA, and confidence in the effect estimates ranged from very low to high. Most RCTs compared various chemoradiation regimes. For other treatment options, such as local excision in early stages or different radiotherapies, we mostly identified comparative cohort studies.

*Conclusion:* Our findings indicate that, in most clinical situations, primary chemoradiation based on 5-FU and MMC is still the gold standard. However, treatment options for stage I anal cancer, particularly of the anal margin, as well as newer treatment approaches should be investigated in future RCTs. Overall, our findings may help health care professionals and patients make informed decisions about treatment choices.



Anal cancer is a rare malignancy contributing to fewer than 3% of gastrointestinal malignant tumours [1]. With 1–2 cases per 100,000 population annually [2], its incidence is low but has been rising in recent years [2–5]. In Europe, 5-year survival is approximately 57% [2]. The most important specific cause is an infection with high-risk HPV types (most commonly HPV 16 or 18) [6,7],

*Abbreviations:* 5-FU, 5-fluorouracil; CCB, capecitabine; CDDP, cisplatin; CFS, colostomy-free survival; CR, complete response; CSM, cancer-specific mortality; CSS, cancer-specific survival; DFS, disease-free survival; EM, early morbidity; ET, early toxicity; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; LM, late morbidity; LT, late toxicity; MD, mean difference; MMC, mitomycin C; OR, odds ratio; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomised controlled trial; RFS, recurrence-free survival; RR, risk ratio; SoF, Summary of Findings; SCCA, squamous cell carcinoma of the anus.

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and risk factors are increased exposure (number of sex partners [6], receptive anal sex [6,8], history of HPV-infections at other genital sites [8–11]) and decreased clearance of HPV (immunodeficiency [12–15], smoking [6,16,17]). Treatment depends on the stage and localisation of the primary tumour.

To inform the development of the national evidence-based guideline on the management of anal cancer in Germany, we conducted a systematic review and meta-analyses of controlled studies on the efficacy and safety of interventions in patients with stage I-III anal cancer, following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [18,19]. This paper aims to appraise and summarise evidence from the review.

## Materials and methods

Our systematic assessment and analysis followed the methods recommended by Cochrane [20] and the GRADE approach [18,19].

### *Protocol and registration*

The key questions (PICOs) and inclusion criteria for primary literature were agreed by the methods group and expert panel of the national guideline [21], the latter of which was representative of the health professionals involved in the management of anal cancer and of affected patients. A protocol of the systematic review was registered at PROSPERO (CRD42019140829, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=140829). In the present article, we only report the results obtained for selected populations (see eligibility criteria).

### *Eligibility criteria*

We included controlled studies assessing the efficacy and safety of interventions for squamous cell carcinoma of the anus (SSCA). With regard to patients, we included those diagnosed with stage I, II or III anal margin or anal canal SCCA and assessed them separately, if possible. In the present report, patients with recurrent or persisting disease after primary treatment, stage IV anal cancer, and immunocompromised patients/patients living with HIV were not included. We included any RCT assessing the included patient populations, regardless of the interventions studied. Non-randomised controlled studies of pre-specified, selected interventions were included if RCTs were not available or contained insufficient information. These interventions were combined chemoradiation, radiotherapy, chemotherapy, local excision of primary tumour, excision of primary tumour and/or locoregional lymph node metastases, chemoradiation with brachytherapy boost, and chemoradiation with hyperthermia. Any of the included interventions, placebo or no therapy could serve as comparators. To be included, studies had to report the results of at least 10 participants who received the same intervention. Languages were restricted to English, German and French. No publication period restrictions were applied.

### *Information sources and study selection*

We searched MEDLINE, Embase and Cochrane CENTRAL on 25 October 2018 and conducted an update search on 18 July 2019. Detailed search strategies for each database are provided in the online supplement (Appendix A.1). Two independent researchers (RNW, MG/GAV) screened titles and abstracts for eligibility and evaluated the full texts of eligible records.

### *Data collection, data items and assumptions*

Data were abstracted independently by two reviewers (RNW, MG/GAV) using a standardised spreadsheet. Disagreements were resolved by re-evaluation and discussion. Data items are specified in Appendix A.2. For time-to-event outcomes, we used the approach reported by Tierney et al. [22] to estimate hazard ratios (HRs) and associated statistics appropriate for random-effects meta-analyses based on HRs reported in publications or, if these were not available, by manually extracting data from survival curves (as long as the number at risk was given). Absolute risks for the GRADE Summary-of-Findings (SoF) tables were calculated using the methods specified by Skoetz et al. [23,24]. For dichotomous outcomes, we used the reported data to calculate risk ratios (RR) or odds ratios (OR), and for continuous outcomes we calculated mean differences (MD). Where possible, we reported 95% confidence intervals. The timing of the outcome assessment was not restricted.

### *Risk of bias and confidence in the effect estimates*

To assess the risk of bias of individual studies, we used the Cochrane Risk of Bias Tool 2.0 (2016) [25,26] for randomised controlled trials and ROBINS-I [27] for non-randomised studies. For each outcome and comparison, our confidence in the effect estimates was quantified using the GRADE approach [18,28]. The GRADE evaluation for each effect estimate comprises a comprehensive appraisal of study design, risk of bias [29], directness [30], consistency [31], precision [32], publication bias [33], and further factors [34]. Table 1 gives an overview of pragmatic interpretations of the GRADE evaluations. The criteria used to up- or downrate the GRADE confidence in the effect estimates are shown in Appendix A.2.

### *Synthesis and presentation of the results*

We used a random-effects model (DerSimonian-Laird) in ReviewManager 5.3 to meta-analyse results if at least two studies reported on the same outcome for the same comparison of interventions.

We reported the data for each comparison in GRADE SoF tables [18]. Where missing information made it impossible to include data in the meta-analyses, we reported data narratively. The detailed results for each comparison, including study characteristics and data on each outcome, are shown in the online supplement (Appendix A.3). In this paper, we report results that could not be included in the meta-analyses only if they differed substantially from results that were included.

A large number of comparisons of interventions were considered when developing the guideline. In this paper, we present the results for the following outcomes only: quality of life (QoL), overall survival (OS), cancer-specific survival (CSS) or mortality (CSM), progression-free survival (PFS), recurrence- or disease-free survival (RFS or DFS), colostomy-free survival (CFS), complete response (CR), early morbidity or toxicity (EM/ET), and late morbidity or toxicity (LM/LT). Data on additional outcomes can be found in the SoF tables (Appendix A.3).

## Results

### *Number of hits and included studies*

The systematic literature search yielded 10,325 (25 October 2018) and 889 hits (update search on 18 July 2019). We identified 33 additional records by manually reviewing the reference lists of existing reviews and guidelines. After excluding duplicates, we screened 7656 titles and abstracts, of which we reviewed 456 in

**Table 1**
GRADE evaluations of the confidence in the effect estimates (modified from Balshem et al. [28]).

| GRADE confidence in the effect estimate | Symbol | Interpretation |
|---|---|---|
| High | ⊕⊕⊕⊕ | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate | ⊕⊕⊕◯ | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low | ⊕⊕◯◯ | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very low | ⊕◯◯◯ | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. |

full text (see PRISMA flowchart in Fig. 1). We ultimately included 41 studies (47 publications), 40 of which reported outcomes that we could include in our meta-analyses.

Three observational studies [35–37], all of which were rated as being at serious risk of bias, compared **local excision alone** to **chemoradiation** in patients with early stage SSCA. The largest of these studies was a registry-based study [35] (*N* = 2243), the other two [36,37] (*N* = 57 and *N* = 25) were retrospective cohort studies. No difference was seen between local excision and chemoradiation with respect to OS [HR 1.07 (0.80–1.44), GRADE: ⊕◯◯◯, 2,300 pts. from 2 studies [35,36]] or PFS [HR 0.94 (0.09–9.44), GRADE: ⊕◯◯◯, 57 pts. from 1 study [36]]. One of these studies reported that there was no significant difference with respect to OS for patients with a primary tumour of less or more than 1 cm diameter [35]. Data on additional outcomes can be found in Appendix A.3, Table 2.

A registry-based study [38] compared **local excision** with **radiotherapy alone**, albeit in patients older than 65 years. The authors applied a propensity score analysis, risk of bias was rated as moderate. No significant differences in OS were found [HR 0.46 (0.20–1.08), GRADE: ⊕◯◯◯, 94 pts [38]].

No comparative studies meeting the eligibility criteria were identified that specifically compared chemoradiation to another intervention **in patients after incomplete excision**.

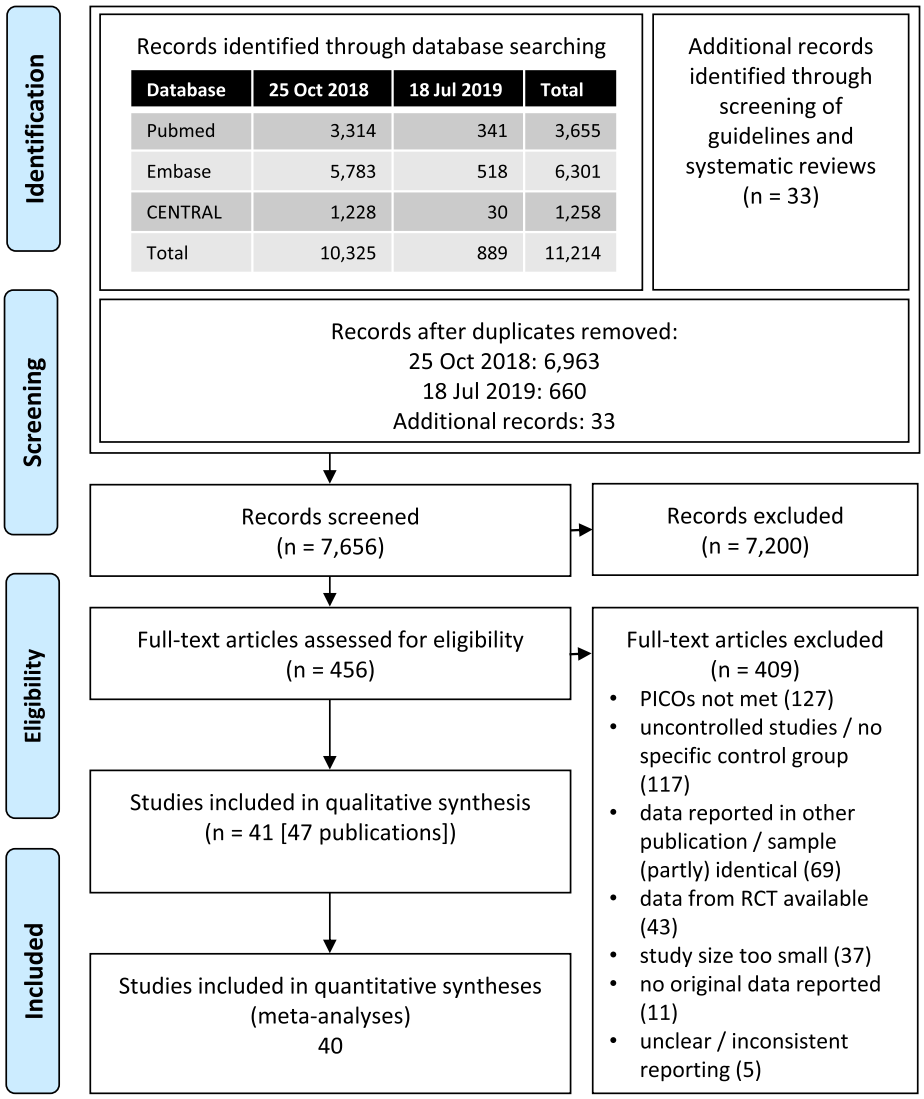


**Fig. 1.** Identification and selection of studies.

We identified two multicentre RCTs [39–41] that compared **chemoradiation** to **radiotherapy alone**. Because these mostly included patients with stage II-III, and a small number of patients with stage I, SCCA, we additionally included three observational studies [42–44] that compared these interventions in patients with stage I-II SCCA.

The observational studies comprised one registry-based study [42] with propensity score analysis (risk of bias: moderate) and two retrospective comparative cohort studies [43,44] (both rated as being at serious risk of bias). In these studies, no significant differences were seen with respect to OS [HR 0.70 (0.48–1.00), GRADE: ⊕◯◯◯, 299 pts aged 55–85 years from 1 study [42]], CSS [HR 0.57 (0.29–1.12), GRADE: ⊕◯◯◯, 445 pts. from 2 studies [42,44]], RFS [HR 0.70 (0.37–1.34), GRADE: ⊕◯◯◯, 445 pts. from 2 studies [42,44]], CFS [HR 1.10 (0.49–2.46), GRADE: ⊕◯◯◯, 299 pts. aged 55–85 years from 1 study [42]; two further studies [43,44] reported heterogeneous results], and LT [RR 1.51 (0.74–3.11), GRADE: ⊕◯◯◯, 146 pts. from 1 study [44]]. Data on additional outcomes can be found in Appendix A.3, Table 5. For OS and RFS, de Bari et al. [43] found that chemoradiation was significantly superior to radiotherapy alone, but we did not include data from the study due to reporting issues.

Of the two RCTs, which mostly included stage II-III SCCA patients, one [39,41] was rated as being subject to 'some concerns', while the other one [40] was rated as being at high risk of bias. A significant advantage was seen for the patients who received chemoradiation with respect to CSM [HR 0.67 (0.51–0.88), GRADE: ⊕⊕⊕◯, 577 pts. from 1 RCT [41]], RFS [HR 0.70 (0.58–0.84), GRADE: ⊕⊕⊕◯, 577 pts. from 1 RCT [41]], CFS [HR 0.71 (0.53–0.95), GRADE: ⊕⊕◯◯, 680 pts. from 2 RCTs [40,41]], and CR [RR 1.49 (1.12–1.99), GRADE: ⊕⊕◯◯, 103 pts. from 1 RCT [40,41]]. No significant difference was found for OS [HR 0.85 (0.70–1.02), GRADE: ⊕⊕◯◯, 680 pts. from 2 RCTs [39,40]]. EM was higher in the chemoradiation group [RR 1.24 (1.03–1.50), GRADE: ⊕⊕⊕◯, 577 pts. from 1 RCT [39]], whereas no significant difference was seen for LM [RR 1.10 (0.90–1.35), GRADE: ⊕⊕⊕◯, 577 pts. from 1 RCT [39]]. Data on additional outcomes can be found in Appendix A.3, Table 6.

We identified one multicentre RCT that compared **chemoradiation with 5-fluorouracil (5-FU) and mitomycin C (MMC)** to **chemoradiation with 5-FU alone** in patients with stage I-III anal canal cancer [45]. In the risk of bias evaluation, this trial was rated as being subject to 'some concerns'. Although both interventions were roughly equivalent (i.e., had narrow confidence interval around the line of no effect) with respect to CR [RR 1.03 (0.92–1.15), GRADE: ⊕⊕⊕⊕, 291 pts. [45]], chemoradiation with 5-FU and MMC was superior with respect to RFS [HR 0.50 (0.33–0.76), GRADE: ⊕⊕⊕⊕, 291 pts. [45]] and CFS [HR 0.59 (0.39–0.90), GRADE: ⊕⊕⊕◯, 291 pts. [45]]. No significant difference was seen for OS [HR 0.76 (0.47–1.21), GRADE: ⊕⊕⊕◯, 291 pts. [45]]. ET was higher in the 5-FU + MMC chemoradiation group [RR 2.88 (1.46–5.69), GRADE: ⊕⊕⊕⊕, 291 pts. [45]], whereas no significant difference was seen with respect to LT [RR 6.95 (0.87–55.80), GRADE: ⊕⊕⊕◯, 291 pts. [45]]. Data on additional outcomes can be found in Appendix A.3, Table 8.

We included two multicentre RCTs that compared **chemoradiation with MMC and 5-FU** to **chemoradiation with cisplatin (CDDP) and 5-FU** [46–49]. Both RCTs were rated as being subject to 'some concerns' in the risk of bias evaluation. The trial ACT II [47,49] was a 2x2 factorial RCT, in which chemoradiation with MMC and 5-FU was compared to chemoradiation with CDDP and 5-FU, each arm divided further into groups with or without maintenance chemotherapy consisting of CDDP and 5-FU. Because outcomes from these (sub)groups were not reported separately, the data we analysed for the comparison of MMC and 5-FU versus CDDP and 5-FU contain data both from patients who received maintenance chemotherapy and those who did not. In the second RCT [46,48], chemoradiation with MMC and 5-FU was compared to chemoradiation with CDDP and 5-FU, the latter following CDDP-based induction chemotherapy. With respect to the outcomes reported in this summary, a significant difference was seen only for DFS: patients who received MMC + 5-FU had an advantage compared with those who received CDDP + 5-FU [HR 0.72 (0.57–0.91), GRADE: ⊕⊕⊕◯, 649 pts. from 1 RCT [48]]. Both interventions were roughly equivalent (i.e., had a narrow confidence interval around the line of no effect) with respect to CR [RR 1.01 (0.97–1.06), GRADE: ⊕⊕⊕⊕, 863 pts. from 1 RCT [49]] and ET [RR 1.05 (0.98–1.12), GRADE: ⊕⊕⊕⊕, 644 pts. from 1 RCT [46]]. No significant differences were seen for OS [HR 0.84 (0.65–1.08), GRADE: ⊕⊕⊕◯, 1589 pts. from 2 RCTs [48,49]], CSM [RR 0.71 (0.39–1.31), GRADE: ⊕⊕⊕◯, 1589 pts. from 2 RCTs [46,49]], PFS [HR 1.05 (0.84–1.33), GRADE: ⊕⊕⊕◯, 940 pts. from 1 RCT [49]], CFS [HR 0.87 (0.71–1.07), GRADE: ⊕⊕⊕◯, 1589 pts. from 2 RCTs [48,49]], and LT [RR 1.25 (0.78–2.00), GRADE: ⊕⊕⊕◯, 625 pts. from 1 RCT [46]]. Data on additional outcomes can be found in Appendix A.3, Table 12.

We identified four comparative cohort studies [50–53] in which a **chemoradiation regimen with MMC and 5-FU** was compared to **chemoradiation with capecitabine (CCB) and 5-FU** in patients with stage I-III anal cancer. These studies included one prospective cohort study [51] (serious risk of bias), and three retrospective cohort studies (two of these [50,52] rated as being at moderate and one [53] rated as being at serious risk of bias). Both interventions were roughly equivalent (i.e., had a narrow confidence interval around the line of no effect) with respect to OS [RR 0.98 (0.89–1.08) after a median follow-up of 2 years, GRADE: ⊕◯◯◯, 100 pts. from 1 study [51]] and CR [RR 1.01 (0.91–1.11), GRADE: ⊕◯◯◯, 205 pts. from 2 studies [51,52]]. With respect to further outcomes reported in this summary, no significant differences were seen: CSS [Peixoto et al. [53] did not find a significant difference; data not meta-analysed due to reporting issues], DFS [HR 1.13 (0.65–1.95), GRADE: ⊕◯◯◯, 300 pts. from 1 study [53]], CFS [HR 0.66 (0.28–1.54), GRADE: ⊕◯◯◯, 300 pts. from 1 study [53]], and ET [RR 0.49 (0.10–2.43), GRADE: ⊕◯◯◯, 105 pts. from 1 study [52]]. Data on additional outcomes can be found in Appendix A.3, Table 16. For OS and RFS, de Bari et al. [43] found that chemoradiation was significantly superior to radiotherapy alone, but we did not include data from the study due to reporting issues.

Two retrospective cohort studies [54,55] at moderate risk of bias compared **chemoradiation with 5-FU and two cycles of MMC** to **chemoradiation with 5-FU and one cycle of MMC** in patients with stage I-III anal cancer. No significant differences were seen with respect to OS [HR 0.83 (0.46–1.49), GRADE: ⊕◯◯◯, 386 pts. from 2 studies [54,55]], CSS [HR 0.32 (0.07–1.42), GRADE: ⊕◯◯◯, 217 pts. from 1 study [54]], PFS [HR 0.85 (0.37–1.92), GRADE: ⊕◯◯◯, 217 pts. from 1 study [54]], DFS [HR 1.17 (0.69–2.01), GRADE: ⊕◯◯◯, 169 pts. from 1 study [55]], CFS [HR 0.91 (0.31–2.67), GRADE: ⊕◯◯◯, 217 pts. from 1 study [54]], ET [RR 0.98 (0.69–1.38), GRADE: ⊕◯◯◯, 217 pts. from 1 study [54]], and LT [RR 0.67 (0.19–2.31), GRADE: ⊕◯◯◯, 217 pts. from 1 study [54]]. Data on additional outcomes can be found in Appendix A.3, Table 18.

We identified one multicentre, 2 × 2 factorial RCT [56] that compared **chemoradiation with and without induction chemotherapy** consisting of CDDP and 5-FU in a sample of stage II-III anal canal cancer patients. The risk of bias was rated as being subject to 'some concerns'. A standard- or high-dose radiotherapy boost was applied in both groups. To compare the induction versus no induction groups, we used pooled data from patients with standard- and with high-dose radiotherapy boost. No significant difference was seen for CFS [HR 0.93 (0.58–1.51), GRADE: ⊕⊕⊕◯, 307 pts.]. Peiffert et al. [56] did not find significant differ-

ences with respect to 5-year OS, CSS, and DFS between the groups of patients who received induction chemotherapy and those who did not. Due to the reporting issues, we did not meta-analyse these data; details and data on additional outcomes are shown in Appendix A.3, Table 20).

We included one multicentre, 2x2 factorial RCT [47,49] that compared **chemoradiation (consisting of either MMC and 5-FU or CDDP and 5-FU) followed by CDDP maintenance chemotherapy** to **chemoradiation (again consisting either of MMC and 5-FU or CDDP and 5-FU) not followed by maintenance chemotherapy** in patients with stage I-III anal cancer. Risk of bias evaluation was 'some concerns'. Because outcomes from the subgroups were not reported separately, the data we present for the comparison contain data both from patients whose main chemotherapy was CDDP-based and those whose main chemotherapy was MMC-based. No significant differences were seen for OS [HR 1.07 (0.81–1.41), GRADE: ⊕⊕⊕◯, 940 pts.], CSS [HR 1.11 (0.80–1.54), GRADE: ⊕⊕⊕◯, 940 pts.], PFS [HR 0.95 (0.75–1.21), GRADE: ⊕⊕⊕◯, 940 pts.], and CFS [HR 0.87 (0.69–1.10), GRADE: ⊕⊕⊕◯, 940 pts.]. Additional data on the outcome 'treatment-associated deaths' can be found in Appendix A.3, Table 22.

One register-based comparative cohort study [57] that was rated as being at serious risk of bias compared **standard-dose (<59.4 Gy)** to **high-dose (≥59.4 Gy) radiotherapy** in patients with stage I-III anal cancer. To be included, patients had to have received concomitant chemotherapy, which was not further specified. No significant difference between the groups was seen with respect to OS [HR 0.95 (0.76–1.19), GRADE: ⊕◯◯◯, 1,349 pts.].

We included eight studies that compared **chemoradiation with intensity-modulated radiotherapy (IMRT)** to **chemoradiation with 3D radiotherapy** in stage I-III anal cancer patients. These included one single-centre RCT [58] (*N* = 20, risk of bias: 'some concerns'), three register-based cohort studies from the US [59–61] (moderate to serious risk of bias), and four single-centre retrospective cohort studies [62–66] (moderate to serious risk of bias). A significant advantage for IMRT was seen with respect to OS [HR 0.86 (0.76–0.98), GRADE: ⊕◯◯◯, 5,246 pts. from 3 observational studies [60–62]; however, Koerber et al. 2014 [66] and Spencer et al. 2014 [63] did not find significant differences between IMRT and 3D radiotherapy – these data were not included in the meta-analysis due to the reporting issues] and CSS [HR 0.74 (0.55–0.99), GRADE: ⊕◯◯◯, 1944 pts. from 2 observational studies [59,60]]. No significant differences were seen with respect to the outcome 'substantial reduction in quality of life' [RR 0.71 (0.32–1.57), GRADE: ⊕◯◯◯, 47 female pts. from 1 observational study [65]], CR [RR 1.00 (0.49–2.05), GRADE: ⊕⊕⊕◯, 20 pts. from 1 RCT [58]], DFS [HR 0.31 (0.09–1.05, GRADE: ⊕◯◯◯, 103 pts. from 1 observational study [64]], and CFS [HR 0.75 (0.07–8.18, GRADE: ⊕◯◯◯, 89 pts. from 1 observational study [62]]. Data on additional outcomes can be found in Appendix A.3, Table 26.

We included a registry-based cohort study [67,68] in which the use of a **radiotherapy boost (5–20 Gy)** was investigated. The study was rated as being at serious risk of bias. In the study, none of the outcomes selected to be reported in this publication were presented. Data on the rate of abdominoperineal resections are shown in Appendix A.3, Table 32.

In a retrospective comparative cohort study [69] that was rated as being at serious risk of bias, **chemoradiation with an integrated radiation boost** was compared to **chemoradiation with a sequential radiotherapy boost**. Patients in the sequential boost group received an overall radiation dose of 59.4 Gy (initially 36 Gy in 20 fractions, and after a break of 16 days, another 23.4 Gy in 13 fractions). In the integrated boost group, patients received an overall dose of 50.4 to 54 Gy in 28 to 30 fractions. Whereas the data on OS and CFS were taken from the propensity-score analysis, the data on local/regional failure, distant metastases, and hematologic toxicity (shown in the Appendix A.3, Table 34) are based on raw rates in the respective groups. No significant differences were seen with respect to OS [HR 1.51 (0.77–2.98), GRADE: ⊕◯◯◯, 190 pts.] and CFS [HR 1.15 (0.65–2.04), GRADE: ⊕◯◯◯, 190 pts.].

We identified one multicentre, 2 × 2 factorial RCT [56] (risk of bias: 'some concerns') that compared **chemoradiation with a high-dose radiotherapy boost** to **chemoradiation with a low-dose radiotherapy boost** in a sample of stage II-III anal canal cancer patients, in both cases with or without induction chemotherapy. To compare outcomes for the high-dose versus low-dose boost groups, we used pooled data that contained patients both with and without induction chemotherapy. Peiffert et al. [56] did not find significant differences with respect to 5-year OS, CSS, and DFS between the groups of patients who received a high-dose versus a standard-dose boost. Due to the reporting issues, these data were not re-analysed. No significant difference was seen for CFS [HR 0.86 (0.53–1.39), GRADE: ⊕⊕⊕◯, 307 pts.]. Details and data on additional outcomes can be found in Appendix A.3, Table 36.

We included four retrospective comparative cohort studies [70–73] that compared **chemoradiation with brachytherapy boost** to **chemoradiation with external beam radiation boost** in patients with stage I-III anal cancer. A further study [74] was not included in the analyses because of a possible substantial overlap of the study populations with one of the included studies [71]. The risk of bias evaluations ranged from critical to moderate. No significant differences were seen with respect to QoL (EORTC QLQ-C30) [MD: −13.5 (−28.63–1.63), GRADE: ⊕◯◯◯, 34 pts. from 1 study [72]], OS [HR 0.62 (0.30–1.31), GRADE: ⊕◯◯◯, 123 pts. from 1 study [73]], CR [RR 1.13 (0.99–1.29), GRADE: ⊕◯◯◯, 165 pts. from 1 study [70]], CSM [RR 1.37 (0.63–2.99), GRADE: ⊕◯◯◯, 162 pts. from 1 study [71]], and CFS [HR 0.66 (0.38–1.15), GRADE: ⊕◯◯◯, 162 pts. from 1 study [71]]. In one study with 81 patients, [72] a significantly lower rate of ET was seen for brachytherapy [RR 0.35 (0.14–0.83), GRADE: ⊕◯◯◯], but no significant difference was seen with respect to LT [RR 0.59 (0.25–1.38), GRADE: ⊕◯◯◯]. Oehler-Janne et al. [72] did not find significant differences with respect to CSS and RFS, but these data were not meta-analysed due to reporting issues. Details and data on additional outcomes can be found in Appendix A.3, Table 38.

We identified two studies that compared **chemoradiation with hyperthermia** to **chemoradiation without hyperthermia** in stage I-III anal cancer patients – one monocentric RCT [75] (*N* = 49) that was rated as being at high risk of bias and one monocentric retrospective comparative cohort study [76] that was rated as being at serious risk of bias. In the RCT, only stage II patients (T2/3 N0 M0) were included. Significant advantages for the application of hyperthermia were found for OS [HR 0.25 (0.07–0.92), GRADE: ⊕◯◯◯, 112 pts. from 1 observational study [76]] and CFS [Ott et al. [76], due to reporting issues, these data were not re-analysed; however, in the RCT [75], a significant advantages was also seen with respect to the rate of colostomies: RR 0.12 (0.02–0.85), GRADE: ⊕⊕⊕◯, 49 pts.]. No significant differences were seen with respect to CSS [HR 0.32 (0.06–1.62), GRADE: ⊕◯◯◯, 112 pts. from 1 observational study [76]], local RFS [HR 0.14 (0.02–1.09), GRADE: ⊕◯◯◯, 112 pts. from 1 observational study [76]; however, in the RCT, [75] a significant advantage was seen, data not included in meta-analysis due to reporting issues], and DFS [HR 0.45 (0.16–1.30), GRADE: ⊕◯◯◯, 112 pts. from 1 observational study [76]]. Details and data on additional outcomes can be found in Appendix A.3, Table 40.

We did not identify any comparative studies that assessed the efficacy and safety of **immune checkpoint inhibitors or other immune therapies** in patients with stage I to III anal cancer.

We identified some further RCTs [77,78] and observational studies [79,80] that assessed data on **various comparisons of**

**interventions**. These data are shown in Appendix A.3, Tables 10, 14, 28 and 30.

## Discussion

In this systematic review, we identified and critically appraised the published evidence on the efficacy and safety of interventions for stage I to III anal squamous cell carcinoma in immunocompetent patients. The quality of the studies was heterogeneous, and their design ranged from retrospective controlled cohort studies to well-conducted RCTs. Observational studies comparing two groups, be it retrospective cohort studies, prospective cohort studies or registry based studies, are inherently prone to selection, allocation and attrition bias. Estimates from these studies may therefore be subject to confounding and should be interpreted with caution. In our review, this is reflected by our GRADE evaluation of confidence in the effect estimates, which was often very low or low for estimates generated from data from observational studies.

Because we assessed a very large number of comparisons and outcomes to inform the development of the German guideline on anal cancer treatment, we could present only a summary of our findings for selected outcomes in this paper. To obtain a comprehensive overview, it is important to consider the Summary of Findings tables in our online Appendix A.3: In some instances, such as the comparison of chemoradiation with induction chemotherapy to chemoradiation without induction therapy, no significant differences were seen with regard to the outcomes presented in this paper, but differences seen for other outcomes and reported only in Appendix A.3, such as hematologic toxicity, may be relevant to patients and therefore important for joint decision making.

Generally, we identified only weak evidence for approaches to treat early stages of anal cancer, making it impossible to identify which approach is best. Although international guidelines [81–84] recommend local excision for stage I anal margin cancer, no controlled studies were available to compare local excision to chemoradiation in this specific population. This being said, we were able to identify observational studies on this comparison, albeit including mostly patients with cancer of the anal canal. In these studies, no significant differences between local excision and chemoradiation were seen for various outcomes, but we rated our confidence in these effect estimates as very low using GRADE methodology. Decisions about how best to treat the early stages of anal cancer, particularly of the anal margin, must therefore continue to be informed primarily by expert experience and consensus.

In contrast, we identified a series of RCTs in which different modalities of chemoradiation were assessed, mostly in stage I to III or stage II to III anal cancer. Combined chemoradiation with 45–59.4 Gy radiation and MMC + 5-FU remains the standard for the treatment of stage II and III anal cancer. Although, radiotherapy alone or chemoradiation with 5-FU alone, with their lower rates of early morbidity/early toxicity, could be a sensible alternative for selected older and/or comorbid patients, combined chemoradiation with MMC + 5-FU was superior with respect to various highly relevant oncologic outcomes such as CR, RFS and CFS. As an alternative combined chemoradiation regimen, MMC may be replaced by CDDP in cases where MMC is contraindicated: For most of the outcomes, no significant difference was seen between combined chemoradiation with MMC + 5-FU compared with CDDP + 5-FU. However, the MMC + 5-FU regimen was significantly superior with respect to DFS, although on the other side, an increased risk of hematologic toxicity was seen. The use of induction or maintenance chemotherapy did not lead to an increase in relevant oncological outcomes such as OS, CSS, or CFS.

We identified evidence from a series of observational studies suggesting that it might be possible to replace 5-FU in the chemoradiation regimen consisting of MMC and 5-FU with capecitabine, which has the advantage of being available as an oral drug. Indeed, no significant differences between the two regimens were seen for important oncological outcomes such as OS, CSS, CR, DFS, and CFS, albeit with confidence in the effect estimates rated as being very low. Similarly, we were not able to identify high-quality evidence on which number of MMC cycles to use. Whereas observational studies did not find significant differences with respect to the main oncological outcomes (OS, CSS, DFS, PFS, CFS), here, too, our confidence in the effect estimates was rates as very low, and some findings suggest that adverse events may be more frequent with two cycles of MMC (i.e., overall toxicity, hematologic toxicity).

The evidence we identified to assess the modalities of radiotherapy within chemoradiation was generally of lower quality than the evidence on modalities of chemotherapy. The results from a registry-based study suggest that using a high dose of radiation ($\geq$59.4 Gy) does not increase OS (very low confidence in the effect estimate). Using IMRT instead of 3D radiotherapy was shown to increase some survival-related outcomes while reducing some side-effects of the radiation. Although we identified only low-quality evidence to support the use of radiotherapy boost, an RCT served as the basis to show that there were no significant differences with respect to OS, DSS, DFS and CFS between a standard-dose (15 Gy) and a high-dose (20–25 Gy) boost.

An interesting approach is the use of deep regional hyperthermia as a supplement to chemoradiation. We identified a small RCT and an observational study that found advantages of this intervention with respect to various relevant oncological outcomes including OS, loco-regional failure and the rate of colostomies. Although there are some limitations to its applicability, particularly in patients with larger or advanced tumours, hyperthermia as an additional intervention should be evaluated in further well-designed studies. One RCT was still being carried out at the time of writing [85].

More recent approaches such as checkpoint inhibitors or other targeted immune therapies have not yet been evaluated in controlled studies in stage I-III anal cancer. Some initial research has been undertaken to assess the response of immune therapies in stage IV and locoregionally advanced stage III anal cancer, [86–88] but well-designed controlled studies are still needed. One randomized study assessing the effect of druvalumab in addition to chemoradiation in locally-advanced anal cancer was still recruiting at the time of writing [89].

Other studies still recruiting participants include the 'Personalising anal cancer radiotherapy dose' (PLATO) trials ACT 3, 4 and 5, which aim to optimise the radiotherapy dose as part of chemoradiation for anal cancer in different stages [90].

## Conclusions

To inform the development of the German national anal cancer guideline, we meta-analysed efficacy and safety data from RCTs and observational studies identified in our systematic review of the literature on treatments for stage I-III anal squamous cell carcinoma. Our results indicate that, in most clinical situations, primary chemoradiation based on 5-FU and MMC is still the gold standard. However, there is sparse evidence for patients with stage I anal cancer, particularly of the anal margin, leading the guideline panel to draw upon clinical experience and expert consensus when they decided on recommendations for these patients. Treatment options for these patients, as well as newer treatment approaches, such as hyperthermia and immune therapy should be investigated

in future RCTs. In addition to informing the decisions of the guideline panel, our results may help health care professionals and their patients make informed decisions about treatment choices.

## Data statement

The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

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## Conflicts of interest

The authors declare that they have no conflicts of interest with regard to the topic discussed in the present manuscript.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.01.031.

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