Comparative Effectiveness Review
Number 273

Treatment of Stages I–III Squamous Cell Anal Cancer: A Systematic Review

Executive Summary

Main Points

- For the initial treatment of stages I–III squamous cell carcinoma of the anus (SCCA), compared with radiation therapy (RT) alone, concurrent doublet chemoradiation (CRT) with 5-fluorouracil (5FU) plus mitomycin (MMC) likely results in greater disease-free survival and lower locoregional failure rate, may result in greater colostomy-free survival, likely increases overall acute harms, may increase hematologic toxicity, and may have no difference in late harms.
- Compared with concurrent CRT with 5FU, CRT with 5FU plus MMC may result in greater disease-free and colostomy-free survival and lower locoregional failure rate but difference in harms remains uncertain.
- Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin likely does not increase overall or progression-free survival and complete response rates, likely does not decrease distant metastasis rate; and may not increase disease-free survival, nor lower locoregional failure rate (up to 5 years of followup), likely decreases the risk of hematologic toxicity, but may not differ in other acute or late harms. Difference in colostomy-free survival remains uncertain.
- Compared with doublet CRT with capecitabine plus MMC, triplet CRT with paclitaxel plus capecitabine plus MMC may increase complete response, overall, disease-free, and colostomy-free survival, and overall acute harms, but may not differ in acute neutropenia, dermatologic, gastrointestinal, or genitourinary toxicity.

Continued on page 2

Agency for Healthcare Research and Quality

- Evidence remains uncertain for other comparisons including local excision versus CRT for stage I cancer; capecitabine versus 5FU; different modalities, doses, volumes, and fractionation schema for RT; dose de-escalation or escalation in CRT; immunotherapy; posttreatment surveillance strategies; and patient-reported outcomes such as bowel, urinary, and sexual function, pain, and quality of life.
- Most of the studies are assessed with high risk of bias. Observational studies should apply advanced methods such as target trial emulation for making causal inferences.
- Patients with immunocompromised status, older age, or minoritized racial/ethnic identities are underrepresented in the available body of evidence.

Background and Purpose

CRT with 5FU plus MMC has remained the standard treatment for stages I–III SCCA for several decades, despite clinical uncertainties and technological advancements. **This systematic review assesses the effectiveness and harms of different strategies for the initial treatment of stages I–III SCCA.** This review, funded by the Patient-Centered Outcomes Research Institute® (PCORI®), will be used by the American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) to develop clinical practice guidelines for the treatment of SCCA.

Methods

We followed the Agency for Healthcare Research and Quality Evidence-based Practice Program methods guidance. Our searches covered publications in MEDLINE®, Embase®, Cochrane Register of Controlled Trials, and ClinicalTrials.gov from January 2000 through March 2024, plus the reference lists of systematic reviews and included studies regardless of publication dates. We included randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) comparing strategies for initial treatment and posttreatment surveillance. We evaluated risk of bias (RoB) using the Cochrane RoB2 tool for RCTs and the ROBINS-I tool for NRSIs, and strength of evidence (SOE) for prespecified outcomes (PROSPERO registration number CRD42023456886).

Results

We included 33 articles from eight RCTs (six with low to moderate RoB and two with high RoB) and 20 NRSIs (serious to critical RoB). Compared with RT alone, CRT with 5FU plus MMC improved several effectiveness outcomes (moderate to low SOE) but increased overall acute harms (moderate SOE) and resulted in no difference in late harms (low SOE, Table A). Compared with CRT with 5FU, CRT with 5FU plus MMC improved several effectiveness outcomes (low SOE), but evidence was insufficient to

compare harms. Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin did not improve several effectiveness outcomes and late harms (moderate to low SOE), lowered acute hematologic toxicity (moderate SOE), and evidence was insufficient and conflicting for colostomy-free survival. Compared with CRT with capecitabine plus MMC, CRT with paclitaxel plus capecitabine plus MMC showed greater overall, disease-free, and colostomy-free survival, and overall acute harms (low SOE). Evidence was insufficient for remaining comparisons (not shown in Table A) including local excision for early-stage cancer, capecitabine versus 5FU, intensity modulated versus three dimensional conformal RT, proton versus photon beam, external beam RT versus brachytherapy boost, different RT doses, volumes, and fractionation schema, induction therapy, maintenance therapy, one versus two cycles of MMC, RT boost versus no boost, immunotherapy, and posttreatment surveillance. Evidence was insufficient for patient-reported outcomes such as bowel, urinary, and sexual function.

Table A. Summary of key findings and strength of evidence

Intervention Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Summary of Individual Study Reported Findings	Strength Of Evidence
CRT with 5FU plus MMC vs. RT alone	Overall survival (up to 5 yrs)	2; RCTs; n=695	No significant difference; precise estimates.	Moderate
	Disease-specific mortality (up to 5 yrs)	1; RCT; n=585	CRT favored over RT alone; rate, 28% vs. 39%, RR of 0.71 (95% CI, 0.53-0.95, median follow up: 42 months and similar in both arms)	Moderate
	CR (6 weeks post treatment)	2; RCTs; n=695	Both RCTs favor CRT over RT alone, rates 80% vs. 54% (p<0.05, n=110); 39% vs.30% (p<0.05, n=585)	Low
	LR failure rate (up to 5 yrs)	2; RCTs; n=695	Both RCTs favor CRT over RT alone, with 5-year rate 32% vs. 50% (p= 0.02, n=110) and 3-year rate 39% vs. 61% (RR, 0.54; 95% CI, 0.42 - 0.69; n=585)	Moderate
	Colostomy-free survival (up to 5 yrs)	1; RCT; n=110	CRT favored over RT alone; estimated improvement by 32% at 5yrs (p=0.002); estimates for each arm not reported	Low
	Overall acute harms	1; RCT; n=585	Significantly greater in CRT (48%) vs. RT alone (38.6%).	Moderate
	Acute hematologic toxicity	2; RCTs; n=695	Significantly greater in CRT vs. RT alone, frequency: 1 vs.0 grade 4 events (n=110); or 20 vs.0 overall events (n=585).	Low
	Acute derm and GI toxicity	2; RCTs; n=695	No significant difference, imprecise estimates.	Low
	Acute GU toxicity	1; RCT; n=585	No significant difference, imprecise estimates	Low
	Overall late harms	1; RCT; n=585	No significant difference, imprecise estimates.	Low
	Late derm toxicity	2; RCTs; n=695	No significant difference, imprecise estimates.	Low
	Late GI and GU toxicity	1; RCT; n=585	No significant difference, imprecise estimates.	Low
CRT with 5FU plus MMC vs. CRT with 5FU	Overall survival (at 4 yrs)	1; RCTs; n=310	No significant difference, precise estimates.	Low
	CR (4-6 weeks post treatment)	1; RCTs; n=310	No significant difference, precise estimates.	Low
	DFS (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 73% vs. 51% (p<0.001).	Low

Intervention Comparison	Outcome	Number of Studies; Study Design; Participants (n)	Summary of Individual Study Reported Findings	Strength Of Evidence
	LR failure rate (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 16% vs 34% (p<0.001).	Low
	Colostomy-free survival (at 4 yrs)	1; RCTs; n=310	Favors 5FU + MMC over 5FU alone, 71% vs. 59% (p = 0.014).	Low
CRT with 5FU plus MMC vs. CRT with 5FU plus cisplatin	Overall survival (up to 5 yrs)	2; RCT; n=1622	No significant difference, precise estimates.	Moderate
	DM (up to 5 yrs)	1; RCT; n=682	No significant difference, precise estimates.	Moderate
	LR failure and DFS (up to 5 yrs)	1; RCT; n=682	No significant difference, imprecise estimates.	Low
	PFS, CR	1; RCT; n=940	No significant difference, precise estimates.	Moderate
	Overall acute harms	2; RCT; n=1622	No significant difference, precise estimates.	Moderate
	Acute hematologic toxicity	2; RCT; n=1622	Significantly greater with MMC vs. cisplatin, with grade 3+ toxicity frequency of 61% vs. 42% (p<0.001, n=682) and 26% vs. 16% (p<0.001, n=940).	Moderate
	Acute derm, GI, and GU toxicity	2; RCT; n=1622	No significant difference, imprecise estimates.	Low
	Late harms	1; RCT; n=682	No significant difference, imprecise estimates.	Low
CRT with capecitabine plus MMC plus paclitaxel vs. CRT with capecitabine plus MMC	Overall survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 95.5% vs 80% (p<0.001).	Low
	Disease-free survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 87.1% vs 64.4% (p=0.001).	Low
	Colostomy-free survival (up to 3 yrs)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 83.2% vs 67.5% (p=0.029).	Low
	CR (at 26 weeks posttreatment)	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 88.9% vs 75% (p=0.049).	Low
	Overall acute harms	1; RCT; n=144	Significantly greater in the paclitaxel arm vs no paclitaxel arm; 56.9% vs 26.4% (p<0.001).	Low
	Neutropenia (grade 3 or 4)	1; RCT; n=144	No significant difference, imprecise estimates.	Low
	Acute derm, GI, GU harms	1; RCT; n=144	No significant difference, imprecise estimates.	Low

Note: Remaining comparisons not mentioned in the table received an insufficient grade. All harms are grade 3 or 4 unless specified otherwise.

Abbreviations: CI- confidence interval; CRT- chemoradiation; LR- locoregional; CR- complete response;; DFS- disease-free survival; PFS- progression-free survival; DM- distant metastasis; 5FU- 5 fluorouracil, MMC- mitomycin C; RT- radiation therapy; derm-dermatologic; GI-gastrointestinal; GU-genitourinary; RCT- randomized controlled trial; yrs- years; vs.- versus; RR- relative risk.

Strengths and Limitations

Our review focused on the highest-quality evidence for benefits and harms of initial treatment strategies from four large databases.

Our review and the evidence itself had limitations. We based our SOE assessment on statistical rather than clinical significance due to the lack of established thresholds for minimal clinically important differences and lack of prioritization of outcomes in this field. RCTs were limited by inconsistency in outcome definitions and measurement between trials, inadequately addressing attrition, multiple comparisons testing, and competing risks over a longer followup period, and inadequate power to compare acute and late harms. Included NRSIs had serious to critical RoB, making it impossible to draw causal inferences. Common limitations of the NRSIs included poorly defined interventions and comparators, lack of power calculations, and inadequately addressing missing data, competing risks, confounding, and potential selection bias. Patients with immunocompromised status, older age, or minoritized racial/ethnic identities were underrepresented, making applicability of findings to these groups challenging.

Implications and Conclusions

For the initial treatment of nonmetastatic SCCA, CRT with 5FU plus MMC is likely more effective but may increase hematologic toxicity compared with RT alone or CRT with 5FU. Compared with CRT with 5FU plus MMC, CRT with 5FU plus cisplatin likely does not improve effectiveness outcomes but likely decreases hematologic toxicity. The addition of paclitaxel as a third cytotoxic chemotherapy drug to CRT with capecitabine plus MMC may increase treatment efficacy and toxicity. Optimal posttreatment surveillance strategies remain uncertain. Future research should prioritize methodological rigor through well-designed RCTs or real-world evidence generation from NRSIs using appropriate methodology such as “target trial emulation” for drawing causal inferences, include patient-reported outcomes such as bowel, urinary, and sexual function, pain, and quality of life, and increase representation of historically underrepresented patients.

Full Report

Parikh RR, Troester A, Southwell B, Ester E, Sultan S, Claussen AM, Greeno E, Arsoniadis E, Church TR, Wilt TJ, Goffredo P, Butler M. Treatment of Stages I–III Squamous Cell Anal Cancer: A Systematic Review. Comparative Effectiveness Review No. 273. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 75Q80120D00008.) AHRQ Publication No. 24-EHC026. PCORI® Publication No. 2024-SR-03. Rockville, MD: Agency for Healthcare Research and Quality. August 2024. DOI: https://doi.org/10.23970/AHRQEPCCER273. Posted final reports are located on the Effective Health Care Program search page.