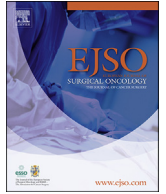




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30-day and long-term outcome following salvage surgery for squamous cell carcinoma of the anus

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ABSTRACT

Introduction: Squamous cell carcinoma of the anus (SCCA) is a rare condition. First line treatment is combined chemo-radio therapy. As many as a third of patients undergoing CRT will experience recurrence. These patients often undergo salvage surgery with an extended abdominoperineal excision. The aims of this study were 1) to assess and evaluate 30-day postoperative morbidity and mortality after salvage surgery for recurrent SCCA, and furthermore, 2) to examine secondary recurrence and long-term mortality after salvage surgery for recurrent SCCA.

Material and methods: Retrospective evaluation of all patients undergoing salvage surgery for SCCA at Copenhagen University Hospital Herlev between 1st of January 2011 and 31th December 2016.

Results: Forty-seven patients were identified. 30-day postoperative mortality was 4%. The most common postoperative complication was perineal wound defects. Within the follow-up period of median 20 (1–80) months, secondary recurrence occurred in 30% of patients. Median disease free survival was 32 months. Secondary recurrence was significantly more frequent in patients with R1 resection and pN \geq 1. Within the follow-up period of median 25 (0–80) months, mortality was 40%. Overall median survival was 39 months. Secondary recurrence was associated with a significantly higher risk of death within the follow-up period.

Conclusion: Salvage surgery for relapse of squamous cell carcinoma of the anus is a safe procedure with a good short-term outcome. Secondary recurrence was more frequent in patients with R1-resection and pN \geq 1. More than one third of the patients died within the follow-up period, and mortality was significantly higher in the group of patients with secondary recurrence.

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Introduction

Squamous cell carcinoma of the anus (SCCA) is a rare condition with a reported annual incidence of 1 in 100,000 [1]. There is a strong correlation between SCCA and human papilloma virus types 16, 18 and 31, as HPV represents the causative agent in 80–85% of patients [2].

First line treatment for SCCA is chemo-radiation (CRT) therapy with concomitant 5-Fluoruracil and Mytomycin combined with fractionated radiotherapy to 50 Gy². Five year mortality in Europe ranges between 44% and 66% [2]. HPV-infection, increasing N- and T-stage, and male sex are known worsening prognostic factors [2–4].

Residual tumor or recurrence of tumor occur in 15–33% of patients after curative intended CRT [4–6]. The recommended treatment of these cases is salvage surgery with an abdominoperineal resection [2,7]. To obtain a R0 resection an extended resection, including resection of bladder/prostate, vagina or sacrum, is necessary in up to two thirds of patients [5]. Thus, reconstruction of the pelvic floor often requires a transpelvine vertical rectus abdominis flap or other flap [5].

SCCA is a rare condition and as a natural consequence the literature on the surgical outcome after salvage surgery for residual or recurrent SCCA is sparse and dominated by studies with small patient populations [4–6,8,9]. The primary aim of this study is to add knowledge on the postoperative course after salvage surgery for SCCA by examining 30-day postoperative complications and mortality. Secondly, to examine long-term mortality and secondary recurrence of disease after salvage surgery for squamous cell anal cancer.

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Material and methods

All patients undergoing salvage surgery for residual or recurrent squamous cell anal cancer at Copenhagen University Hospital Herlev between January 1st, 2011 and December 31st, 2016 were identified. Herlev Hospital is the tertiary referral center for SCCA in eastern Denmark, covering approximately 2.6 million citizens.

Electronic patient journals were retrospectively reviewed and the following variables were recorded: age, sex, WHO performance score, ASA-score, smoking habits, alcohol consumption, comorbidities, preoperative treatment, time from preoperative treatment to surgery, type of surgery, surgical pathology, 30-day postoperative complications, secondary recurrence, location of secondary recurrence and mortality. R0 resection was defined as cancer-free resection margins of ≥ 1 mm⁷.

30-day postoperative complications were classified according to the modified Clavien-Dindo score [10]. Complications with a Clavien-Dindo score ≤ 2 were classified as a minor and score ≥ 3 were classified as major. Comorbidities were registered as existing if medically treated on admission.

We planned to investigate the effect of an R1-resection as well as lymph node positive disease on the risk of secondary recurrence. Dichotomous variables where compared using the Fishers exact test. For all analyses, a p value below 0.05 was considered statistically significant. Overall and disease free survival were presented by Kaplan-Meier curves. Statistical calculations where performed using SPSS software version 19. The study was approved by the Danish Data Protection Agency; journal number 05368 ID-nr.: HGH-2017-016.

Results

Forty-seven patients were identified. Median age was 59 years and 57% of the patients were female. The most common salvage procedure performed was an abdominoperineal excision and reconstruction of the pelvic floor with a transpelvine VRAM-flap. R0-resection was accomplished in 85% of the cases. Further demographics and surgical data are shown in Table 1.

There were two deaths within the 30-day postoperative period, one due to cardiac arrest and one due to a pulmonary embolism. The most common complication was wound-defect, occurring in 32% of the cases. Most of these were perineal and classified as minor. Further 30-day postoperative complications are shown in Table 2.

Median follow up for disease free survival after salvage surgery for SCCA was 20 months (range, 1–80 months). Within the follow up period, fourteen (30%) patients experienced secondary recurrence. Median disease free survival was 32 months. Secondary recurrences primarily occurred within the first two years after salvage surgery (Fig. 1). The most frequent locations for secondary recurrence were inguinal lymph node (6 cases) and neo-perineum (4). Less frequent locations included the peritoneum (2), small bowel (1) and collum femoris (1). Secondary recurrence occurred in 23% (9/40) of patients after an R0 resection versus 71% (5/7) of patients after an R1 resection ($p = 0.018$). The same pattern was seen according to pathological N-staging with secondary recurrence in 23% (9/40) of patients with pN0 versus 71% (5/7) of patients with pN ≥ 1 ($p = 0.018$).

Median follow up for postoperative death was 25 months (range, 0–80 months). Within the follow-up period 19 (40%) died, and eight of these deaths were related to SCCA. Median overall survival after salvage surgery was 39 months (Fig. 2). Mortality was significantly higher in the group of patients with secondary recurrence (12/14 (86%) vs. 7/33 (21%); $p < 0.0010$ deaths within the follow-up period, respectively). Time from secondary recurrence to death was median (range) 8 (1–35) months.

Table 1
Demographics and surgical data.

	(N = 47)
Age (median)	59 (43–82)
Sex (F:M)	27:20 (57%/43%)
Preoperative treatment	
None	3 (6%)
CRT	28 (60%)
Radiation	16 (34%)
Time from preoperative treatment to surgery (Median, min-max)(n = 45)	273 days (34–4179)
ASA-score	
1	18 (38%)
2	23 (49%)
3	6 (13%)
4	0
Performance-score	
0	18 (38%)
1	17 (36%)
2	12 (26%)
3	0
4	0
Active tobacco use (n, %)	15 (32%)
Alcohol ($\leq 7/14$ units/week)	7 (15%)
Comorbidities	
Cardiac ^a	18 (38%)
Pulmonary ^b	2 (4%)
Endocrine ^c	19 (40%)
HIV	1 (2%)
Other ^d	10 (21%)
Procedure	
Abdominoperineal excision	31 (66%)
Abdominoperineal excision including the posterior wall of the vagina	13 (28%)
Abdominoperineal excision including os coccygis	1 (2%)
Abdominoperineal excision including hysterectomy and bilateral salpingo-oophorectomy	1 (2%)
Reconstruction of perineal defect	
Transpelvine VRAM-flap ^e	26 (55%)
Transpelvine VRAM-flap including reconstruction of the vagina	16 (34%)
Local flap	4 (9%)
Suture	1 (2%)
TNV stage	
T	
pT0	3 (6%)
pT1	7 (15%)
pT2	22 (47%)
pT3	10 (21%)
pT4	5 (11%)
N	
pN0	40 (85%)
pN1	6 (13%)
pN2	1 (2%)
V	
pV0	42 (89%)
pV1	5 (11%)
R0-resection	40 (85%)
Postoperative length of stay (median)	15 days (2–84)

^a Biologic heart valve, hypertension, atrial fibrillation, angina pectoris.

^b c. pulmonis operata, asthma.

^c Hypothyroidism, hyperthyroidism.

^d Osteoporosis, Crohns disease, hypercholesterolemia, nephropathy, breast cancer.

^e Vertical rectus abdominis muscle.

Discussion

In this report presenting one of the largest number of cases from a single tertiary referral center with secondary recurrence and salvage surgery for squamous cell carcinoma of the anus, we found few complications in the postoperative period and a low postoperative mortality rate. Furthermore, long-term survival is achievable and is closely related to a R0 resection, which

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