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Quality of life following salvage surgery for squamous cell carcinoma of the anus

T.B. Pedersen*, A.F. Juvik, S.F. Koren, P. Gocht-Jensen, M.F. Klein

Department of Surgery, Copenhagen University Hospital Herlev, Herlev Ringvej 75, 2730, Herlev, Denmark

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ABSTRACT

Introduction: Squamous cell carcinoma of the anus is a rare condition. First line treatment is combined chemo-radio therapy. As many as a third of patients undergoing chemo-radiotherapy will experience recurrence. These patients often undergo salvage surgery with an extended abdominoperineal excision. The aim of this study was to examine the quality of life in disease free survivors following salvage surgery for squamous cell carcinoma of the anus.

Material and methods: Patients undergoing salvage surgery for SCCA at Copenhagen University Hospital Herlev between 1st of January 2011 and 31st December 2016 were identified and quality of life was assessed with EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires.

Results: 47 patients underwent salvage surgery for relapse or residual tumor in the period. From this cohort 25 disease-free survivors were identified. Fourteen (56%) patients returned a completed questionnaire. Overall median global health status was 75(range 20–100). Functional scores were generally high. In General, symptom scores were low, however all men reported impotence with a median symptom score of 100(range 67–100) and half the women reported dyspareunia. Urinary impairment was present in half the patients. Abdominal and buttock pain scores were low.

Conclusion: Quality of life following salvage surgery for squamous cell carcinoma of the anus is affected but at an acceptable level. However, there are considerable side-affects in the form of impotence, dyspareunia and urinary impairment.

Introduction

With a reported annual incidence of 1 in 100.000 [1], squamous cell carcinoma of the anus(SCCA) is a rare condition. Marginal T1 tumors can be treated with surgical excision, but in the majority of cases first line treatment is combined chemo-radiation therapy(CRT), which leads to complete tumor regression in 80–90% of cases [2]. Overall five year survival ranges between 44 and 78% [2]. Infection with human papilloma virus represents the causative agent in 80–85% of cases [2].

In the case of residual tumor or recurrence of disease, the treatment is salvage surgery with an extended abdominoperineal resection, which often also includes reconstruction of the perineum and posterior wall of the vagina with a flap of the vertical rectus abdominis muscle [3] (VRAM-flap). The most common postoperative complication following salvage surgery is minor wound defects [3,4]. 30-day postoperative mortality ranges between 0 and 2% [3,5]. Secondary recurrence of SCCA following salvage surgery is seen in 31–36% [3,4]of cases, and is often related to an R1-resection. Overall 5 year survival following salvage surgery for SCCA is relatively high and ranges between 61 and 67% [3,4]. Thus, a large proportion of these patients are cured of their cancer, however, to our knowledge there are no studies available describing the quality of life following salvage surgery for SCCA.

The aim of this study was to examine the quality of life in patients with long-term disease free survival following salvage surgery for SCCA.

Material and Methods

Patients undergoing salvage surgery for SCCA at Copenhagen University Hospital Herlev, the tertiary referral center for SCCA in eastern Denmark, between January 1st, 2011 and December 31st, 2016 were identified. To achieve a homogenous sample as possible, only disease free survivors were included in the study.

* Corresponding author.
E-mail address: torben.pedersen28@gmail.com (T.B. Pedersen).

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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 salvage surgery to QoL questionnaire, type of surgery and surgical pathology. R0 resection was defined as cancer-free resection margins of $\geq$1 mm. Comorbidities were registered as existing if medically treated at the time of surgery.

Assessment of quality of life was performed with the European Organization for Research and Treatment of Cancer Quality of life Questionaires QLQ-C30 [6] and QLQ-CR29 [7]. QLQ-C30 is a validated integrated system for assessing health related quality of life in cancer patients, including five functional scales, three symptom scales, a global health status scale and six single items. QLQ-CR29 is a supplement to the QLQ-C30 system designed for use in colorectal cancer patients. Although SCCA and colorectal cancer are different diseases, we believe there are similarities in their long-term postoperative course. To our knowledge there are no SCCA specific EORTC modules available, thus we found it reasonable to use this supplement module. QLQ-CR29 consist of five functional scales and eighteen symptom scales. All scales range between 0 and 100, and a high scale score represents a higher response level. Thus, a high functional score and global health status score represents a healthy level of functioning and a high symptom score represents a high level of symptoms, respectively. Furthermore, patients were encouraged to list any issues regarding their quality of life they felt had not been addressed in the questionnaires.

All patients were contacted by phone ahead of receiving the questionnaires and informed about the questionnaire and encouraged to participate in the study. Patients that had not returned the questionnaire after two months were contacted by phone again and encouraged to participate.

To identify differences between groups, Mann–Whitney and $\chi 2$ tests were performed for continuous and dichotomous variables, respectively. P values ≤ 0.05 were considered statistically significant. 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.

Table 1
Demographics and surgical data.

	Responders (N = 13[a])	Non-responders (N = 12)	p-value
Age at surgery (median, range)	53 (45–82)	58 (43–80)	0.77
Sex(F:M)	6:7 (46%/54%)	7:5 (58%/42%)	0.54
Days from salvage surgery to questionnaire (Median, range)	1473 (456–2303)	988 (406–2555)	0.23
ASA-score at surgery			0.79
• 1	5 (38%)	4 (33%)	
• 2	7 (54%)	6 (50%)	
• 3	1 (8%)	2 (17%)	
• 4	0	0	
Performance-score			0.98
• 0	7 (54%)	6 (50%)	
• 1	5 (38%)	5 (42%)	
• 2	1 (8%)	1 (8%)	
• 3	0	0	
• 4	0	0	
Active tobacco use (n, %)	5 (38%)	4 (33%)	0.79
Alcohol ($\leq$7/14 units/week)	2 (15%)	1 (8%)	0.56
Comorbidities			
• Cardiac[b]	7 (54%)	4 (33%)	0.30
• Pulmonary[d]	0	0	1.0
• Endocrine[c]	2(15%)	3 (25%)	0.55
• HIV	1(8%)	0	0.33
Procedure			0.20
• Abdominoperineal excision	7 (54%)	7 (58%)	
• Abdominoperineal excision including the posterior wall of the vagina	6 (46%)	4 (25%)	
• Abdominoperineal excision including os coccygis	0	1 (8%)	
Reconstruction of perineal defect			0.44
• Transpelvine VRAM-flap[d]	6 (46%)	8 (67%)	
• Transpelvine VRAM-flap including reconstruction of the vagina	6 (46%)	4 (33%)	
• Local flap	1 (8%)	0	
TNV stage			
T			0.62
• *p*T0	0	2 (17%)	
• *p*T1	3 (23%)	3 (25%)	
• *p*T2	7 (54%)	5 (42%)	
• *p*T3	2 (15%)	1 (8%)	
• *p*T4	1 (8%)	1 (8%)	
N			0.95
• *p*N0	12(92%)	11 (92%)	
• *p*N1	1 (8%)	1 (8%)	
• *p*N2	0	0	
V			0.29
• *p*V0	13 (100%)	11 (92%)	
• *p*V1	0	1 (8%)	
R0-resection	13 (100%)	11 (92%)	0.29

[a] One questionnaire could not be linked to demographic data.
[b] Hypertension, atrial fibrillation, angina pectoris.
[c] Diabetes, thyroid disease.
[d] Vertical rectus abdominis muscle.

Results

47 patients underwent salvage surgery for recurrent disease or residual tumor in the period. From this cohort, 25 disease-free survivors were identified. All received the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaire. Fourteen (56%) patients returned a completed questionnaire, one did not fill out identification and could not be linked to demographic data.

For responders of the questionnaire median age at time of surgery was 53 years (range 45–82), median time from salvage surgery to questionnaire was 1473 days (range 456–2303) and 92% were reconstructed with a VRAM-flap. Further demographic and surgical data for responders and non-responders are shown in Table 1. As shown, responders and non-responders did not differ significantly with regard to demography and surgical course.

Table 2
QLQ-C30 Quality of life scores ranging 0–100. High global health/QOL and functional scales indicate healthy level of functioning and high symptom scales indicates high level of symptoms.

	N(%) reporting symptom	Median score	Range
Global health status/QoL		75	20–100
Functional Scales			
Physical functioning	–	83	20–100
Role Functioning	–	75	0–100
Emotional Functioning	–	100	25–100
Cognitive Functioning	–	100	33–100
Social Functioning	–	100	33–100
Symptom Scales			
Fatigue	12(86%)	28	0–100
Nausea and Vomiting	4(29%)	0	0–67
Pain	6(43%)	0	0–100
Dyspnoea	1(7%)	0	0–67
Insomnia	6(43%)	0	0–100
Appetite loss	4(29%)	0	0–100
Constipation	2(14%)	0	0–67
Diarrhoea	4(29%)	0	0–100
Financial difficulties	5(36%)	0	0–100

Table 3
QLQ-CR29 Quality of life scores ranging 0–100. High global health/QOL and functional scales indicate healthy level of functioning and high symptom scales indicates high level of symptoms.

Functional Scales	N(%) reporting symptom	Median score	Range
Body Image	–	50	0–100
Anxiety	–	100	0–100
Weight	–	100	0–100
Sexual Interest(male)	–	67	33–100
Sexual Interest(female)	–	0	0–33
Symptom Scales			
Urinary frequency	9(64%)	25	0–100
Blood and mucus in stool	4(29%)	0	0–33
Stool frequency	6(43%)	0	0–100
Urinary incontinence	7(50%)	17	0–100
Dysuria	2(14%)	0	0–67
Abdominal pain	4(29%)	0	0–100
Buttock pain	7(50%)	17	0–100
Bloating	9(64%)	33	0–100
Dry mouth	11(79%)	33	0–100
Hair loss	3(21%)	0	0–67
Taste	4(29%)	0	0–67
Flatulence	6(43%)	0	0–100
Fecal incontinence	8(57%)	33	0–100
Sore skin	5(36%)	0	0–100
Embarrassment	6(43%)	0	0–100
Stoma care problems	1(7%)	0	0–33
Impotence	8(100%)	100	67–100
Dyspareunia[a]	1(17%)	0	0–100

[a] One patient listed she was single and therefor would not know, two listed “it is impossible”.

Overall median(range) global health status was 75(20–100). In general, functional scales were high and symptom scales were low, indicating a healthy level of functioning and a low level of symptoms. The primary exceptions were a reported low sexual interest for women and high symptom scores for impotence and dyspareunia in men and women, respectively. Complete scores for the EORTC QLQ-C30 and QLQ-CR29 questionnaires are listed in Tables 2 and 3. Seven patients listed further issues regarding their quality of life. Three patients listed perineal herniation/heaviness, making sitting down for longer periods difficult. One reported he felt his penis had shrunken since the operation. Five patients listed that intercourse was impossible or that they suffered from impotence. One listed to be very afflicted by urinary incontinence. Two stated that all-though they had side-effects to salvage surgery their quality of life was better after surgery than before.

Discussion

In this, to our knowledge first, report to investigate quality of life in long-term disease-free survivors following salvage surgery for squamous cell carcinoma of the anus we found rather high functional scales and low symptom scales, with an exception in sexual function as all men reported impotence and the majority of women reported dyspareunia.

The median global health status score in this study was 75. The EORTC mean global health status reference value for recurrent cancer [8] is 56. Having in mind that this patient group undergoes a long curative course of chemo-radiotherapy, with a well-documented impact on the QoL a range of side-effects in the form of fecal and urinary incontinence and decreased sexual desire [9–11], before undergoing major surgery for recurrent disease we believe this is an acceptable and expectable global health score.

The most significant symptom reported in this study was male impotence. All male patients reported impotence with a median symptom score of 100 (range 67–100). As all male patients also reported high sexual interest with a median functional score of 67 (range 33–100), this has the potential to cause frustration and decrease quality of life. For women the median symptom score for dyspareunia was 0. Two patients left blank answers in the questionnaire and commented that “it is impossible” and one that she was single and therefore did not know, hence the symptom score for dyspareunia should most likely be higher. All women reported a low functional score in sexual interest, median 0 (range 0–33), indicating low sexual interest, which probably is less likely to cause frustration or decreased quality of life. The majority of patients reported some degree of altered urinary frequency, with a median symptom score of 25 (range 0–100). Also, urinary incontinence was observed in half of the patients with a median symptom score of 17 (range 0–100). In abdominoperineal excisions performed for low rectal adenocarcinomas the same pattern of urinary impairment, impotence, dyspareunia and loss of sexual interest has been observed in studies examining the QoL following extralevatory abdominoperineal excision (ELAPE) for rectal cancer [12,13]. The extended abdominoperineal excision performed in order to obtain a R0 resection for SCCA recurrence is a major procedure and avoidance of iatrogenic lesions of the pudendal and splanchnic nerves, causing impotence, less/loss of genital sense of touch and urinary impairment, is probably not possible. Furthermore, the patients sexual life and urinary function is affected by CRT [9–11] before they undergo salvage surgery, therefore we do not find this surprising.

Surprisingly, abdominal pain was only reported in four cases, with a median symptom score of zero (range 0–100). Buttock pain was reported in half the cases, with a median symptom score of 17(range 0–67). Although three patients reported perineal heaviness/herniation making sitting for longer periods hard, the

reconstruction of the perineum with a VRAM-flap seems well tolerated. The same pattern was observed in a large database study involving 245 patients undergoing ELAPE for rectal cancer, reporting long-term perineal pain in 38% and perineal hernia formation in 2% of cases, respectively [14].

Dry mouth was reported by eleven (79%) patients, with a median symptom score of 33(range 0–100). Kamali et el [12] reported dry mouth after both extralevatory abdominoperineal and standard abdominoperineal excision for rectal cancer. Whereas there is no reports of dry mouth following CRT [9–11]. Another common symptom in this cohort was fatigue, reported by eighty six percent of the patients with a median symptom score of 28(range 0–100). Fatigue is also reported with a mean symptom score ranging from 25 to 32 following extralevatory and standard abdominoperineal excisions [12]. Although we have no causative explanation to the high incidence of dry mouth and fatigue, it could be related to the surgery.

The creation of a stoma is inevitable when undergoing salvage surgery for SCCA. Approximately half the patients reported fecal incontinence, sore skin, flatulence or embarrassment of their stoma, with median stoma symptom scores ranging from 0 to 33. At the same time, the stoma seems well tolerated as only one patient reported stoma care problems. This pattern can also be observed in Kamali et al.'s study of quality of life following extralevatory and standard abdominoperineal excision for rectal cancer and in a recent [15] study comparing QoL in patients undergoing either sphincter preserving surgery or definitive colostomy for adenocarcinoma of the lower or middle rectum.

Primary limitations of the present study include the retrospective design, limited sample size and low questionnaire answer percent of fifty-six. Especially the low response rate is worrying, as this may bias results in both positive and negative direction. However, when comparing the demographic and surgical data for responders and non-responders there is no apparent difference in the two groups, which makes it reasonable to assume that the results of this study is covering for the entire cohort. Strengths include the validity of data from a single tertiary referral center where staging, CRT and follow up for salvage surgery are performed in a uniform manner, and the detailed information on the postoperative course as well as the long median follow-up.

In conclusion, the overall long-term quality of life following salvage surgery for SCCA is acceptable in disease-free survivors. However, severe side effects in the form of impotence, dyspareunia and urinary impairment are common. There is an obvious need for further studies examining the quality of life following salvage surgery for SCCA. In the future patients should be informed preoperatively of the most common side-effects, and in the postoperative follow-up there should be focus on handling and minimizing side-effects affecting QoL.

Conflict of interest statement

The authors have no financial conflict of interest.

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