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Survival following surgical treatment for anorectal melanoma seems similar for local excision and extensive resection regardless of nodal involvement

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ABSTRACT

Background: Anorectal melanoma is a rare malignancy with a dismal prognosis. The purpose of this study was to investigate whether the survival per stage is influenced by the surgical approaches (local excision or extensive resection), to assess prognostic factors of survival, and to answer the question whether the practiced surgical approaches changed over time.

Methods: Dutch cancer registry organizations (IKNL and PALGA) were queried for all patients with a diagnosis of anorectal melanoma (1989–2019). Patients with disseminated disease at diagnosis were excluded. Survival outcomes were compared for the two surgical approaches stratified by stage (clinical node negative (cN0) and clinical node positive (cN+)) and date of diagnosis.

Results: A total of 103 patients were included in this study. In both cN0 and cN+ patients the surgical strategy did not significantly influence survival (cN0: 21.7% 5-year survival, median 25 months for local excision versus 13.7% 5-year survival, median 17 months for extensive resection ($p = 0.228$), cN+: 11.1% 5-year survival for local excision, median 17 months versus 8.7% 5-year survival, median 14 months for extensive resection ($p = 0.741$)). Stage and date of diagnosis showed to be prognostic factors of survival. The ratio between the two surgical approaches was unchanged over three decades.

Conclusions: Extensive resection does not seem to improve survival in both cN0 and cN+ anorectal melanoma patients compared to local excision. However in the past three decades no shift towards local excision has been found. cN+ stage and an older date of diagnosis are predictors for worse survival.

1. Introduction

Anorectal melanoma is a rare malignancy. It accounts for 0.4–1.6% of all malignant melanomas [1]. In the Netherlands, 247 anorectal melanomas were diagnosed from 1989 to 2019, resulting in an incidence of 4.8 per 10 million persons per year [2]. Due to the rare nature of this disease, no standardized diagnostic and therapeutic protocols exist. Therefore, it is not clear whether the widely used more radical surgery by means of an extensive abdominoperineal resection results in better survival compared to local excision.

In anorectal melanoma, patients usually present with local symptoms like rectal bleeding, an anal mass, anal pain or a changed defecation pattern [1,3]. At the time of initial diagnosis, almost 60% of patients already have distant metastases [1]. This contributes to the very poor prognosis of anorectal melanoma with a 14% 5-year survival rate and a median survival of 15 months in the Netherlands [2], which is in contrast to the relatively good prognosis of cutaneous melanomas that are associated with a 92% 5-year survival [4].

Currently, there is no consensus regarding the optimal treatment of anorectal melanoma per stage. Surgery may improve the prognosis of patients with local and locoregional anorectal melanoma, but does not seem to prolong the survival of patients with disseminated disease [5]. Therefore, except for a few cases where surgery is needed for palliative reasons, disseminated anorectal melanoma is treated with best supportive care without surgical intervention.

The available and practiced surgical approaches for locoregional disease are local excision and extensive resection (like abdominal perineal resection (APR) and since 2009 total mesorectal excision (TME)) [6,7]. Local excision is a much less invasive approach and has gained popularity by the introduction of TEM (transanal endoscopic microsurgery) and TAMIS (transanal minimal invasive surgery) techniques and devices since 2007 [8]. An extensive resection is a much more

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invasive procedure which also implies that the pararectal lymph nodes are removed during the procedure. Disadvantages of this approach are a longer hospital stay and rehabilitation period. Another disadvantage of the extensive resection procedure is a much higher complication rate; in particular wound infections and readmission, but also voiding dysfunction and sexual dysfunction can occur [9–11]. In addition, the subsequent burden of a colostomy can have significant impact on quality of life [12]. These are important issues in patients that might have a short life ahead of them.

The purpose of this study is to investigate whether the survival per stage is influenced by the two most applied surgical approaches (local excision and extensive resection), to assess prognostic factors of survival and to answer the question if the distribution of the practiced surgical approaches changed over time.

2. Methods

The Netherlands Comprehensive Cancer Organisation (IKNL) and the nationwide network and registry of histo-and cytopathology in the Netherlands (PALGA) were queried for all patients with a diagnosis of anorectal melanoma. The available IKNL (April 2019 release) and linked PALGA (March 2020 release) data from 1989 to 2019 were used [2,13]. The included patients met the following criteria: histologically diagnosed as melanoma (Histologic type ICD-O-3 codes 8720–8780) and rectum or anus as anatomic site (primary site codes C20–C21).

Different descriptions for surgical techniques were categorized into two groups, namely: local excision and extensive resection. Local excision includes: local tumor excision, endoscopic resection, and transanal endoscopic microsurgery. Extensive resection includes the more extensive surgical approaches with pararectal lymph node removal: abdominal perineal resection and total mesorectal excision. For the aim of this study patients were divided into two categories based on above-mentioned surgical approach (local excision and extensive resection).

Tumor stage was categorized into three groups; node negative disease, node positive disease and distant disease. Node negative disease was defined as a tumor confined entirely to the anorectum or a tumor infiltrated into the surrounding tissue, without involvement of regional lymph nodes. Node positive disease was defined as tumor involvement of regional lymph nodes. These regional lymph nodes are defined as lymph nodes that are located along the providing vessels of the anorectum, according to the American Joint Committee on Cancer (AJCC) [14]. Distant disease was defined as metastases in distant organs or distant lymph nodes. The patient cohort did not contain surgical procedures that included an initial inguinal nodal dissection for inguinal nodal disease. The clinical stage was recorded as the conclusion of the radiologic work-up that could have differed per patient and could be based on inguinal ultrasound, rectal endoscopic, ultrasound, CT, PET and/or MRI scanning.

Patients with distant disease, an unknown clinical stage and patients who underwent no surgical procedure or an unknown surgical procedure were excluded for this study.

2.1. Analyses

Characteristics of the patient (sex, age, date of diagnosis, stage, location, time between diagnosis and surgery) were analyzed for differences between the local excision group and the extensive resection group. For the clinical node negative (cN0) and clinical node positive (cN+) groups differences in date of diagnosis, sex, age and location were analyzed. The Independent T-Test was used to analyze parametric continuous data, Fischer's exact test or chi-square test was used to analyze categorical variables. Kaplan-Meier survival tables and survival curves were plotted to display survival rates over time. Survival was compared using log-rank statistics.

Univariable and multivariable Cox regression analysis was used to assess prognostic factors of survival for the different surgical techniques. Survival was defined as the number of months between the date of diagnosis and the date of death. Factors significant at a 10% significance level in univariable analysis were included in the multivariable analysis. Enter method was used to identify independent predictors.

All the statistical analyses were conducted using SPSS software (IBM SPSS Statistics for Window version 24.0). All tests were 2-sided, confidence intervals were set at 95%, and a p-value of 0.05 or less was considered to be statistically significant.

3. Results

The IKNL database included a total of 246 patients that met the inclusion criteria. After excluding patients with an unknown clinical stage (n = 60), distant disease (n = 64) and patients who underwent no surgical procedure (n = 19) a total of 103 patients were included for analysis. Local excision was performed in 57 patients and 46 patients underwent extensive resection. A comparison of patient characteristics between the local excision and extensive resection group is shown in Table 1. Sex was not different between groups (p = 0.841). The mean age in the local excision group was 70, in the extensive resection group 64 (p = 0.028). Of patients with cN0 disease, 48 underwent local excision and 23 underwent an extensive surgical resection. Of patients with cN+ disease, 9 underwent local excision and 23 underwent extensive resection (p < 0.000). Also differences in tumor location and time between diagnosis and surgery were statistically significant between both groups, with more anal than rectal melanoma in the local excision group (p = 0.005) and a shorter period to surgery for local excision in comparison to extensive resection (27 versus 54 days, p < 0.000). Table 1 also shows that the distribution between the surgical approaches did not

Table 1
Patient characteristics according to type of surgery.

Variable	No. of patients (%)		p
	Local excision	Extensive resection	
N	**57**	**46**	
Sex			
Male	22 (54)	19 (46)	0.841*
Female	35 (56)	27 (44)	
Age (years)			
Mean (SD)	70 (±15)	64 (±12)	0.061**
<60	14 (48)	15 (52)	
60-75	17 (46)	20 (54)	
>75	26 (70)	11 (30)	
Date of diagnosis			
Mean (SD)	2008 (±7)	2007 (±7)	0.809**
1990–1999	8 (57)	6 (43)	
2000–2009	21 (55)	17 (45)	
2010–2019	28 (55)	23 (45)	
Stage			
cN0	48 (68)	23 (32)	**<0.000****
cN+	9 (28)	23 (72)	
Location			
Rectal	21 (42)	29 (58)	**0.005****
Anal	33 (73)	12 (27)	
Combination of rectal and anal	3 (38)	5 (62)	
Time between diagnosis and surgery (days)			
Mean (SD)	27 (±33)	54 (±28)	**<0.000****
0-30	29 (91)	3 (9)	
31-60	8 (35)	15 (65)	
>60	8 (40)	12 (60)	
Missing	12 (43)	16 (57)	
Follow up (months)			
Median (IQR)	21 (36)	15 (7)	0.087**

* Fischer's exact.
** Independent T-Test.
*** Chi-square test.
Abbreviations: cN0: clinical node negative; cN+: clinical node positive; SD: standard deviation; IQR: interquartile range.

change over three decades (55–57% local excision versus 43–45% extensive resection). Of 48 patients with cN0 disease who underwent local excision initially, 10 (21%) underwent a subsequent extensive resection after a median of 4 months. The reason was a non-radical excision in all of these patients. Of the 9 patients with cN+ disease who underwent local excision initially, 1 (11%) underwent a subsequent extensive resection after one month due to irradicality.

Differences between the clinical and pathological stage are shown in Table 2 for patients who underwent extensive resection. For patients with cN0 disease who underwent resection, 26% had positive nodes on pathological examination. In patients with cN+ disease, this was pathologically confirmed in 91% of the cases. Sex, age, date of diagnosis and tumor location were not associated with discrepancy between clinical and pathological nodal status ($p > 0.05$).

3.1. Survival

Survival rates of anorectal melanoma are shown in Table 3. The estimated 1- and 3-year survival for all patients with (non-distant) anorectal melanoma was 70.7% and 25.0%, the median survival was 18 months. For cN0 stage anorectal melanoma the estimated 1- and 3-year survival was 71.6% and 32.3% with a median survival of 21 months, which was significantly better in comparison to cN+ stage anorectal melanoma whereas the estimated 1- and 3-year survival was 68.8% and 9.4% with a median survival of 14 months ($p = 0.015$, Fig. 1A). There were no significant differences in survival between both surgical procedures in the cN0 group ($p = 0.228$) and cN+ group ($p = 0.741$) (Fig. 1B). For cN0 patients, median survival was 25 months for those who underwent local excision, 17 months for those who underwent extensive resection and 21 months for those who underwent a subsequent extensive resection after initial local excision ($p = 0.409$, Fig. 1C, Table 3).

Survival seemed to improve over time. For patients diagnosed with anorectal melanoma in 1990–1999 the median survival was 13 months (estimated 1- and 3-year survival 64.3% and 14.3%), for patients diagnosed in 2000–2009 the median survival was 17 months (estimated 1- and 3-year survival 63.2% and 18.4%) and for patients diagnosed in 2010–2019 median survival was 20 months (estimated 1- and 3-year survival 86.1% and 33.1%) (Table 3, Fig. 1D).

Variables potentially associated with survival (sex, age, date of diagnosis, stage, location, type of surgery and time between diagnosis and surgery) were analyzed in the univariable Cox regression analysis (Table 4). Factors associated with worse survival on univariable analysis were extensive resection (Hazard Ratio (HR) 1.53, $p = 0.051$ compared to local excision) and cN+ stage (HR 1.76, $p = 0.017$ compared to cN0 stage), while earlier date of diagnosis showed a HR 0.97 for each additional year, $p = 0.085$. In addition, tumor location was associated with survival, with a HR 0.62, $p = 0.037$ for anal tumors compared to rectal tumors.

On the multivariable analysis (Table 4), only stage and date of diagnosis showed to be independent predictors of survival with a hazard ratio of 0.97 for date of diagnosis ($p = 0.035$), demonstrating a better survival in more recent year of diagnosis, and a hazard ratio of 1.68 ($p = 0.035$) for cN+ stage compared to cN0 stage, demonstrating a worse survival for cN+ disease. Type of surgery and tumor location were not significantly associated with survival in the multivariable model.

Table 2
Clinical and pathological nodal staging in patients who underwent extensive resection.

	Extensive resection N	Pathological stage	N (%)
cN0	23	**pN0**	17 (74%)
		pN+	6 (26%)
cN+	23	**pN0**	2 (9%)
		pN+	21 (91%)

Abbreviations: cN0: clinical node negative; cN+: clinical node positive; pN0: pathological node negative; pN+: pathological node positive.

Table 3
Percentage of overall survival.

	6 months	1 year	2 years	3 years	5 years	Median (IQR)
All patients	95.1	70.7	39.0	25.0	15.0	18 (24)
cN0	95.8	71.6	48.4	32.3	18.9	21 (39)
Local excision (n = 48)	95.8	75.0	53.8	36.6	21.7	25 (44)
Local excision only (n = 38)	94.7	68.4	57.6	38.4	23.0	25 (48)
Local excision + subsequent extensive resection (n = 10)	100.0	100.0	40.0	30.0	20.0	21 (24)
Extensive resection (n = 23)	95.7	63.9	36.5	22.8	13.7	17 (22)
cN+	93.8	68.8	18.8	9.4	9.4	14 (12)
Local excision (n = 9)	88.9	66.7	22.1	11.1	11.1	17 (15)
Extensive resection (n = 23)	95.7	69.6	17.4	8.7	8.7	14 (12)
Date of diagnosis						
1990–1999 (n = 14)	92.9	64.3	28.6	14.3	7.1	13 (25)
2000–2009 (n = 38)	94.7	63.2	36.8	18.4	10.5	17 (21)
2010–2019 (n = 51)	96.1	86.1	43.5	33.1	20.6	20 (38)

Abbreviations: cN0: clinical node negative; cN+: clinical node positive; IQR: interquartile range.

4. Discussion

Anorectal melanoma is a rare and aggressive type of cancer. The present study shows a median survival of 18 months for patients that were treated with curative intent for local and locoregional disease. More radical and extended surgery with lymph node removal did not result in survival gain compared to local excision only in both cN0 and cN+ anorectal melanoma patients. However, during the past three decades no shift towards local excision could be seen. cN+ stage and an older date of diagnosis turned out to be negative predictors of survival.

Other studies that were published so far on this topic were all performed on epidemiologic data and showed comparable results for locoregional anorectal melanoma patients. In the study of Chen et al. [5] and Iddings et al. [15], both based on the SEER (Surveillance Epidemiology and End Results) database, survival after local excision was comparable to extensive resection. In the study of Chen (2016) [5] a total of 76 patients with cN0 disease were included. The median overall survival was 26 months in the local excision group, 13 months in the extensive resection group ($p = 0.153$). A total of 34 patients with cN+ were included. The median overall survival in the local excision group was 7 months and 11 months for the extensive resection group ($p = 0.087$). Iddings et al. (2010) [15] included 143 patients with locoregional anorectal melanoma in which 51 patients underwent APR and 92 underwent transanal excision. Median overall survival was similar in both groups: 18 and 16 months respectively ($p = 0.775$). This study made no stage distinction and did not perform analyses to assess prognostic factors of survival. The most recent study of Ford et al. (2018) [6] including 570 patients compared local resection with APR and the data were extracted from the National Cancer Database of America (NCDB). The study also made no distinction between stages and is therefore difficult to compare with the results in this study, but overall there was no significant difference in 5-year survival (abdominoperineal resection 21% vs local resection 17%; $p = 0.310$).

The study of Choi et al. [16] describes a better survival for patients who underwent APR in comparison to local excision (64.1 months vs.

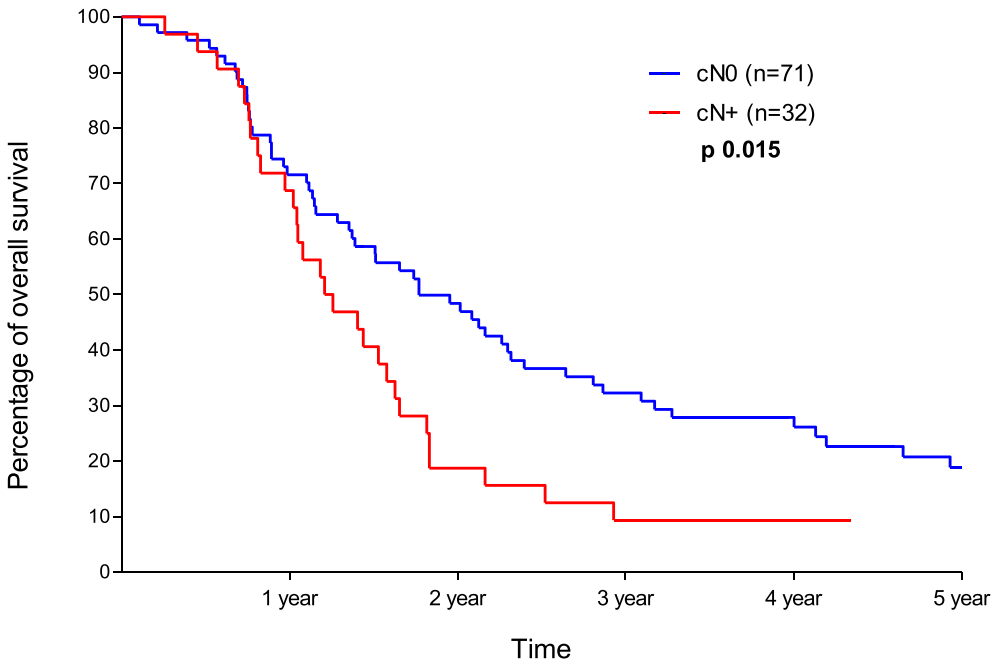

Fig. 1A. Kaplan Meier curves of patients with cN0 disease compared to patient with cN+ disease. Abbreviations: cN0: clinical node negative; cN+: clinical node positive.

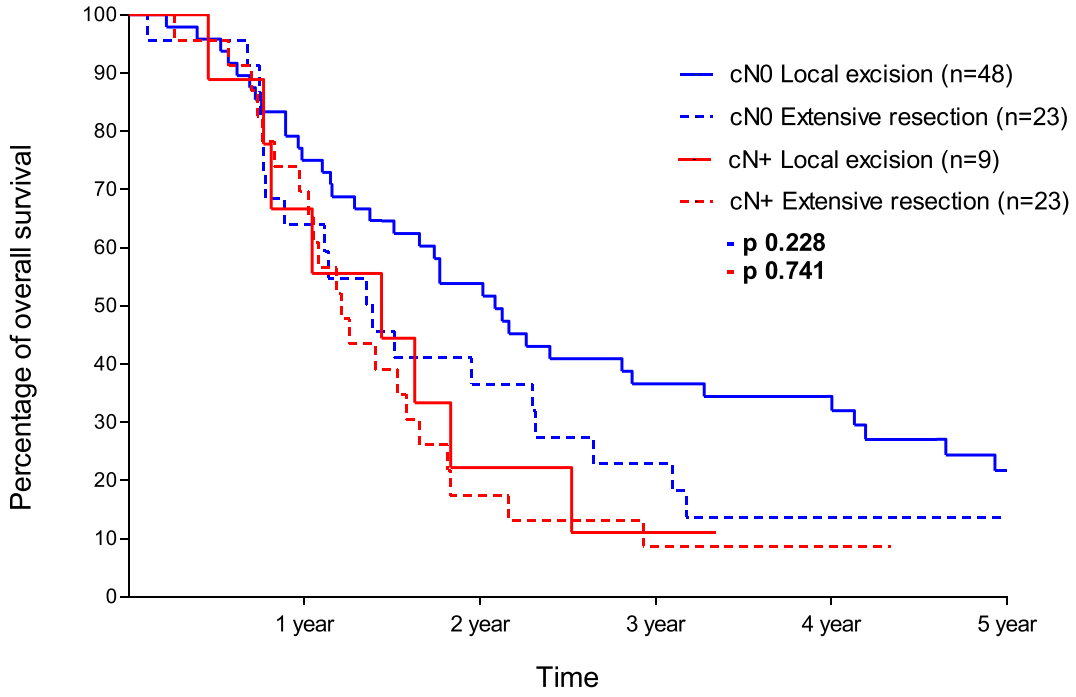

Fig. 1B. Kaplan Meier curves of patients who underwent local excision compared to patients who underwent extensive resection stratified by nodal stage. Abbreviations: cN0: clinical node negative; cN+: clinical node positive.

10.9 months, $P < 0.001$). However, this study has been conducted with a very small patient cohort only including 19 patients. Other studies with small patient numbers did not show any discernible difference in survival between local excision and abdominoperineal resection [17–19].

Remarkable is that a previous study from the Netherlands by Roumen [20] analyzed 63 anorectal melanoma cases and already concluded in 1996 that "patients with local disease should, whenever possible, undergo a local procedure, since a more radical and mutilating approach does not lead to a better long-term survival, while more short-term morbidity and discomfort can be expected". Despite this conclusion and the conclusions of most abovementioned studies, the present study did not find a decrease of extensive resections in the Netherlands over time.

The two negative predictors of survival found in this study were cN+ stage and older date of diagnosis. The negative impact of cN+ stage is the strongest, which is similar for other cancers. For the impact of date of diagnosis, improved survival over time might be due to earlier diagnosing (the Dutch colorectal screening program started in 2014 [21]),

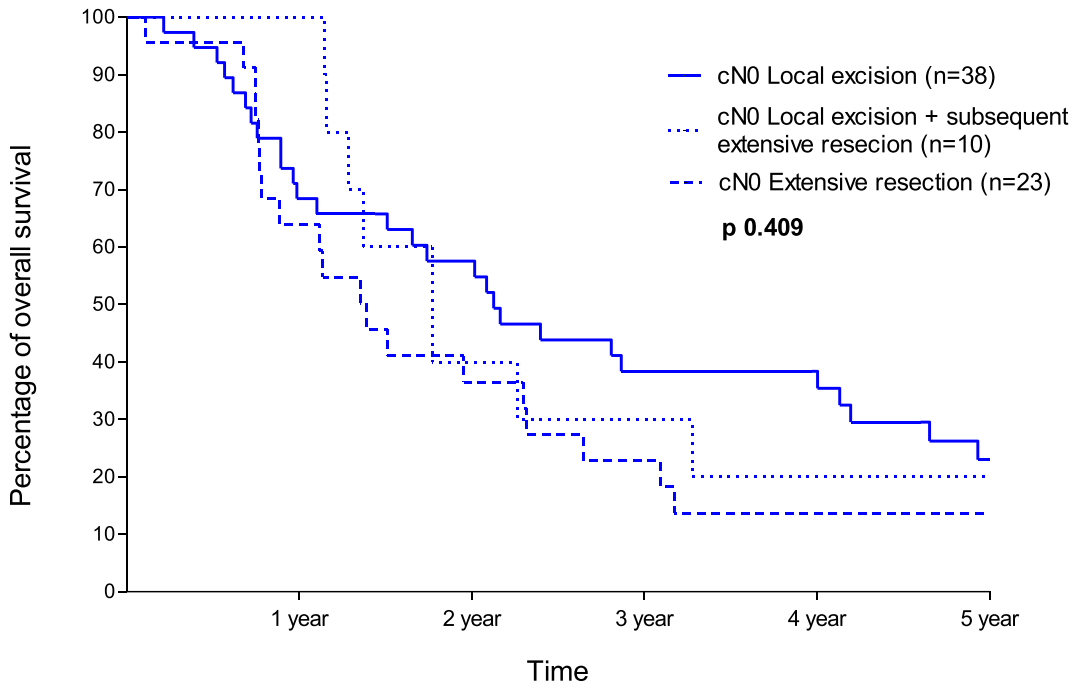

Fig. 1C. Kaplan Meier curves of cN0 patients who underwent only local excision, local excision + subsequent extensive resection and extensive resection; Abbreviations: cN0: clinical node negative.

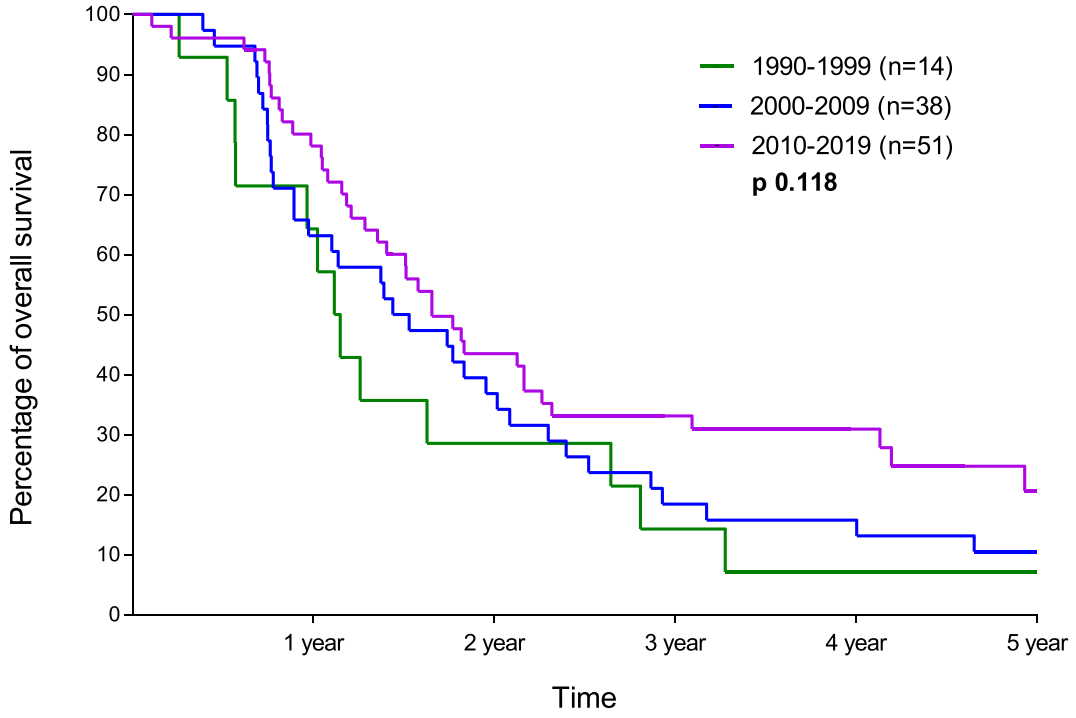

Fig. 1D. Kaplan Meier curves of patients with anorectal melanoma stratified by date of diagnosis.

better staging (more widely use of the PET/CT since 2008 [22]), and/or improvement of quality of surgery (rise of TME surgery since 2009 [7]) and systemic therapies over time. For the fact that 26% of the cN0 patients turned out to be node positive on pathological examination, sub-optimal staging is a possible explanation as well. Unfortunately, the data cannot define whether the preoperative work-up included MRI and/or PET/CT-scanning.

This retrospective database study has a number of limitations to discuss. First, this is a retrospective study based on epidemiologic data that depends on accurate coding, especially for the stage and type of surgery. A significant proportion of patients had to be excluded. Therefore, and due to the rareness of the disease, the cohort size is relatively small for a 30-year database. Also, the codings used by the IKNL and surgical procedures are evolving and sometimes changed over years. However, this shortcoming has been overcome by creating two treatment groups and clear stages of disease, and by comparing the IKNL data with the PALGA data which enabled checking pathology reports with the reported type of surgery.

Table 4
Cox regression analysis of prognostic factors; an HR > 1 indicates a worse survival.

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex						
Male	1					
Female	1.08	0.71–1.67	0.705			
Age						
Continuous	1.01	0.99–1.02	0.880			
<60	1					
60-75	0.73	0.43–1.24				
>75	1.04	0.61–1.76				
Date of diagnosis						
Continuous	0.97	0.94–1.00	**0.085**	0.97	0.94–1.00	**0.035**
1990–1999	1					
2000–2009	0.73	0.39–1.36				
2010–2019	0.54	0.29–1.00				
Stage						
cN0	1					
cN+	1.76	1.11–2.79	**0.017**	1.68	1.00–2.82	**0.035**
Location						
Rectal	1			1		
Anal	0.62	0.39–0.97	**0.037**	0.69	0.43–1.12	0.137
Combination of rectal and anal	0.86	0.39–1.91	0.710	0.85	0.37–1.93	0.691
Type of surgery						
Local excision	1					
Extensive resection	1.53	1.00–2.34	**0.051**	1.15	0.71–1.86	0.577
Time between diagnosis and surgery (days)						
Continuous	1.00	0.99–1.01	0.745			
0-30	1					
31-60	1.47	0.82–2.62				
>60	0.76	0.39–1.48				

Abbreviations: cN0: clinical node negative; cN+: clinical node positive; HR: hazard ratio; CI: confidence interval.

Secondly, a few important issues were not recorded in the database. Details on the preoperative work-up to define the clinical stage of disease were not specified in the data which may have led to the heterogeneity of the cohorts and also medical comorbidity was not recorded in the database. These factors might have influenced the surgical strategy. Also, data on postoperative outcomes, complications of the surgical procedure, local control in palliative procedures, adjuvant therapy and postoperative quality of life are missing.

Thirdly, there is no data available of the rationale for choosing the surgical approach. This may have led to a selection/treatment bias, whereby for example younger and mostly more vital patients underwent more often a resection. Also there is no data on the patient's symptoms, preferences, and even palliative considerations that guided the treatment choices; e.g. if patients present themselves with disabling fecal incontinence, an extensive resection could be a better option than a local excision. However, we cannot reconstruct a scenario in which this selection bias could fully jeopardize the survival distribution between the subgroups.

In the absence of a clear survival benefit of extensive resection in comparison to local excision, quality of life and time of recovery after the surgical procedure merits consideration. After a local excision procedure, patients are expected to have a one day or overnight hospital stay, and generally have a very quick recovery with early resumption of normal activities and normal diet [23]. After an extensive resection procedure, patients are expected to have around a week (5–13 days) hospital stay, and need a much longer recovery period before returning to normal activities and normal diet [12]. This recovery period until full fitness is generally more than 6 months [24], which are valuable months when the median survival is only 18 months. Reviewing the existing literature, quality of life is worse after extensive resection in comparison to local excision: especially role function, body image, and micturition-related problems are worse, and male patients are more likely to experience sexual problems after extensive resection than after local excision [25,26]. Due to these factors and the similar survival of the surgical approaches, local excision should be in general the preferred technique for the treatment of anorectal melanoma in our opinion.

Currently, the effect of non-surgical treatments like targeted therapies, immunotherapy, chemotherapy, or radiation therapy is not clear, but developments on systemic therapies are rapidly expanding. Mutations related to anorectal melanoma have been identified [27–33], and the advantages of administration of (neo)adjuvant targeted therapies on survival seems promising [34–38], but need to be subject to further clinical research. For cutaneous melanomas it is known they are highly immunogenic, however, the same has not been shown yet in anorectal or other mucosal melanomas [39]. Compiled subset data among clinical trials on immunotherapy even seems to suggest a decreased response in mucosal melanoma compared to cutaneous melanoma, but further investigations on this subject are necessary [39–41]. The use of chemotherapy seems reserved to palliative treatment and it is doubtful whether it improves survival in anorectal melanoma [42,43]. Only a few studies on radiation therapy for anorectal melanoma have been conducted, all describing only small numbers of patients. These small series did not show any benefit on survival or local recurrence rate for anorectal melanoma [44,45].

Staging is the backbone of pre-operative work-up and the most optimal staging procedure should be defined. In our opinion, staging should include MRI for locoregional staging and PET/CT for detection of metastases, conform the staging for rectal adenocarcinoma [46]. Follow-up should be performed through MRI and PET/CT as well. Based on the present results and data of abovementioned previous studies we think that a local excision should be offered to cN0 and even cN + anorectal melanoma patients when this is technically feasible and a sufficient functional outcome is expected. Finally, a national standardized approach should be created for this rare and aggressive type of melanoma in order to get some grip on its behavior and to analyze and optimize treatment strategies. In addition, being a rare cancer, it would be our recommendation to create a national or even international registry to monitor local control, recurrent disease, and survival following surgical treatment of anorectal melanoma.

5. Conclusion

Anorectal melanoma is a highly lethal disease. The two different surgical strategies in both cN0 and cN+ stage anorectal melanoma did not result in a difference in prognosis. Extensive resection did not seem to result in survival gain compared to local excision based on these retrospective epidemiologic data. Therefore, depending on the tumor invasion and patient symptoms, local excision could be the better approach, saving quality of life in patients with a short prognosis.

Optimal staging should be defined and performed and (inter)national guidelines on anorectal melanoma treatment should be defined and their effects on local control and survival monitored. Future research will have to focus on newer modalities such as immunotherapy and targeted therapies in order to improve survival.

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Author contributions statement

E. Jutten, MD, LLM: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing - original draft, writing - review and editing.

S. Kruijff, MD, PhD: conceptualization, methodology, supervision, validation, writing - review and editing.

A.B. Francken, MD, PhD: conceptualization, supervision, writing - review and editing.

H.L. van Westreenen, MD, PhD: conceptualization, supervision, writing - review and editing.

K.P. Wevers, MD, PhD: conceptualization, data curation, formal analysis, methodology, project administration, supervision, validation, writing - review and editing.

Declaration of competing interest

None.

The authors hereby declare that this article is not under consideration for publication elsewhere and that the publication is approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyrightholder.

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