Epidemiology And Prognosis Factors Of Primary GI Melanoma In The Past Decade: Results From The SEER Database

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Research Article

Keywords:

Posted Date: March 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1440134/v1

Abstract

Background: Primary malignant melanomas of the Gastric mucosa are uncommon. Most cases of Gastrointestinal (GI) melanomas are secondary, arising from metastasis at distant sites. GI melanomas have been associated with dismal prognosis, owing to their identification at more advanced stages. The purpose of this study is to investigate the clinical characteristics, survival outcomes, and prognostic factors of patients with primary GI melanoma in the past decade.

Methods: A total of 399 patients diagnosed with Primary GI melanoma, between 2008 and 2017, were ultimately enrolled in our study by retrieving the Surveillance, Epidemiology, and End Results (SEER) database. We analyzed demographics, clinical characteristics, and overall mortality (OM) as well as cancer-specific mortality (CSM) of primary GI melanoma. Variables with a p value < 0.1 in the univariate Cox regression were incorporated into the multivariate Cox model to determine the independent prognostic factors, with a hazard ratio (HR) of greater than 1 representing adverse prognostic factors.

Results: From a sample of 399 primary GI melanomas, male gender (56.4%), age range 60-79 years (52.88%), non-Hispanic whites (70.18%), as well as annual income of $75,000+ yearly (30.33%) were the most represented. Crude analysis revealed higher overall mortality (OM) in age group 80+ (HR = 4.042, 95% CI 1.732 - 9.433, p = 0.001), stomach location of the tumor (HR = 3.261, 95% CI 1.658 - 6.417, p = 0.001), distant metastases (HR = 2.967, 95% CI 2.22 - 3.965, p=0), Nonmetropolitan counties not adjacent to a metropolitan area (HR= 2.211, 95 % CI 1.253-3.9, p=0.006), and chemotherapy (HR= 1.417, 95% CI 1.078-1.863, p=0.012). Crude analysis for Cancer specific mortality (CSM) also revealed higher mortality in the same groups. Multivariate cox proportional hazard regression analyses only revealed higher OM in age group 80+ (HR = 5.653, 95% CI 2.212 - 14.445, p=0), stomach location of the tumor (HR = 2.821, 95% CI 1.265 - 6.292, p = 0.011), and distant metastases (HR= 4.491, 95% CI 3.115-6.476, p=0). Multivariate cox proportional hazard regression analyses of CSM also revealed higher mortality of the same groups.

Conclusion: Primary GI melanoma is a rare entity. Only a few studies have been carried out in recent years to evaluate factors affecting the survival and mortality of primary GI melanoma. The paucity of data on primary GI melanoma governed the need of this study. In this population-based retrospective cohort study using the SEER database, we found that age at diagnosis, the primary site of the disease, and advanced disease at diagnosis were independent factors predicting poor prognosis. Furthermore, even surgical resection did not significantly impact the overall mortality or the cancer-specific mortality. This cohort paves the path for further prospective studies identifying individuals at an increased risk of primary GI melanomas, earlier and closer screenings in such individuals, and then evaluation of long-term prognosis in these patients as age and advanced disease were both independent risk factors predicting poor prognosis in our study.

1. Introduction

Melanoma accounts for approximately 6% of all primary cancers in the United States. Most melanoma cases are cutaneous in origin [1]. When present in the Gastrointestinal (GI) tract, melanomas are thought to originate from primary cutaneous origin [2].

To date, only a few cases of Primary GI melanomas have been reported in the literature and are believed to arise from ectopic melanocytes [3–9]. The incidence of Primary GI melanoma is low in that it only represents 2–15% of all cases of GI melanomas [10].

Based on prior literature, there have been very few studies that have addressed the survival outcome of patients with primary GI melanoma. The study by Zheng et al, that enrolled patients from 1975 to 2016, is one of the largest studies addressing the epidemiological characteristics of Primary GI melanomas [11]. The study demonstrated that while the incidence of primary GI melanomas has been increasing since 1975, they are still rare and are detected at advanced stages [11]. However, there is still a paucity of conclusive data and a lack of adequately powered studies properly defining epidemiology characteristics, survival outcomes, and prognostic factors of patients with Primary Gastrointestinal (GI) melanoma over the past decade alone.

We used a nationally representative database to evaluate the independent prognostic factors amongst patients with primary GI melanomas. While there has been a stable number of yearly new diagnoses of Primary GI melanoma over the past decade, we believe there has been a higher mortality in patients with primary gastric location. We hope that this study will pave the path for future larger cohort studies in regard to evaluating the prognostic factors associated with primary GI melanomas and factors impacting survival outcomes in these patients.

2. Methods

2.1 Study design

A population-based retrospective cohort study of patients with Primary GI melanoma was conducted using the SEER research plus data, 18 registries, Nov 2020 submission database (http://www.seer.cancer.gov). The SEER Program is one of the largest and most authoritative sources of the cancer-related dataset in the United States, which is sponsored by the United States National Cancer Institute (US NCI). The SEER 18 database collects cancer incidence, patients' clinicopathological features, and survival data from 18 population-based cancer registries and covers nearly 28% of the U.S. population [12].

2.2 Data selection

Inclusion Criteria:

All patients with primary GI melanoma diagnosed from 2007 to 2018 were selected in our cohort based on, (1) Primary site [c15.0 to c21.8 and c26 to c26.9] and (2) histological type [8720 to 8790] [11]. The

above-mentioned ICD-9 and/or ICD-10 codes were used to extract data regarding these patients from the SEER database.

Exclusion Criteria:

We excluded patients with an unknown age at diagnosis, race, or stage of the GI melanoma.

2.3. Study Variables

Main exposure

Tumor site is the main predictor of mortality in this study. Tumor sites were classified into stomach, anus, colon, small intestine, esophagus, rectum, and others.

Outcomes

Overall mortality

Patients who died of any causes at end of the study were categorized as “yes”, and those who did not were categorized as “no”.

Cancer-specific mortality

Patients who died of primary GI melanoma at the end of the study were categorized as “yes”, and those who died of other causes were classified as “no”.

Survival months

For overall mortality, survival time was calculated from the date of diagnosis to the date of death, or the date of last follow-up (December 31, 2017) as reported in the SEER registry. For the cancer-specific mortality, survival time was calculated from the date of diagnosis to the date of GI Melanoma related death, or the date of last follow-up as recorded in the SEER registry.

Sociodemographic and tumor characteristics

Variables such as age at diagnosis, gender, race (White, Black, and others), origin (Non-Hispanic and Hispanic), year of diagnosis, primary site of tumor, histological type, stage at diagnosis (localized, regional, and distant), geographic residential area, yearly income,marital status, year of diagnosis, surgery and radiation, as well as chemotherapy were extracted. Histologic characteristics were categorized as melanoma not otherwise specified (NOS), nodular melanoma, spindle cell melanoma NOS, mucosal lentiginous melanoma, and others. “Malignant melanoma, NOS " indicates no tumor subtype in patient records.

2.4 Statistical analysis

Cox proportional hazard regression model is based on the assumption that hazard rates are proportional over time. Variables with value < 0.1 in the univariate Cox regression model were incorporated into the multivariate Cox proportional analysis to determine the independent prognostic factors associated with OM and CSM, with a hazard ratio (HR) > 1 representing adverse prognostic factors. All tests were two-sided, with a confidence interval set as 95% and p value < 0.05 deemed statistically significant. All statistical tests were performed by using Software STATA 16.1.

3. Results

A total of 399 patients with primary GI melanoma were included in our study. The general demographic and clinicopathological characteristics of this cohort are summarized in Table 1. The male gender (56.14%), age range 60–79 (52.88%), non-Hispanic whites (70.18%), counties in metropolitan areas of 1 million people (63.41%), and yearly income $75,000+ (30.33) were the most represented groups in our cohort. The most encountered primary site was the anus (51.88%), which represented more than half the cases. Malignant melanoma NOS (86.97%) was the most common histologic type, and spindle cell melanoma NOS (1.25%) was the least common. The majority of diagnoses were made at the advanced disease stage, with distant metastases (41.35%). Married patients constituted the majority of the study (53.13%), followed by widowed patients (20.05%). Most patients did not undergo surgical resection (84.71%) or receive chemotherapy (79.45%). There was a steady of steady number of new cases from 2008 to 2017 with an average of 40 new cases per year.

Table 1
Demographic and Clinicopathologic characteristics of US patients with Primary GI melanoma between 2008 and 2017.

Characteristics		
	N=	%
Total	399	100
Gender		
Male	224	56.14
Female	175	43.86
Age at diagnosis, y.o		
0–39	14	3.51
40–59	100	25.06
60–79	211	52.88
80+	74	18.55
Race		
Non-Hispanic white	280	70.18
Non-Hispanic black	19	4.76
Hispanic	64	16.04
Other	36	9.02
Cancer Site		
Anus	207	51.88
Colon	10	2.51
Esophagus	17	4.26
Rectum	130	32.58
Small intestine	17	4.26
Stomach	12	3.01
Other	6	1.50
Histologic Subtype		
Malignant Melanoma, Not otherwise specified	347	86.97
Nodular melanoma	34	8.52

Characteristics		
Spindle cell melanoma, Not otherwise specified	5	1.25
Mucosal lentiginous melanoma	6	1.50
Other	7	1.75
Tumor stage		
Localized	127	31.83
Regional by direct extension only	25	6.27
Regional lymph nodes involved only	49	12.28
Regional by both direct extension and lymph node involvement	33	8.27
Distant	165	41.35
Living area		
Counties in metropolitan areas of 1 million persons	253	63.41
Counties in metropolitan areas of 250,000 to 1 million persons	72	18.05
Counties in metropolitan areas of 250,000 persons	32	8.02
Nonmetropolitan counties adjacent to a metropolitan area	28	7.02
Nonmetropolitan counties not adjacent to a metropolitan area	14	3.51
Income per year		
$< $35,000	6	1.50
$35,000–44,999	28	7.02
$45,000–54,999	65	16.29
$55,000–64,999	87	21.80
$65,000–74,999	92	23.06
$75,000+	121	30.33
Marital Status		
Married	212	53.13
Single	58	14.54
Divorced/separated	29	7.27
Widowed	80	20.05
Unknown	20	5.01

Characteristics		
Surgery and Radiation		
Yes	61	15.29
No	338	84.71
Chemotherapy		
Yes	82	20.55
No	317	79.45
Year of diagnosis		
2008	34	8.52
2009	46	11.53
2010	34	8.52
2011	30	7.52
2012	38	9.52
2013	32	8.02
2014	50	12.53
2015	50	12.53
2016	39	9.77
2017	46	11.53

Crude analysis of factors associated with all-cause mortality and Primary Gastrointestinal Melanoma related mortality among US patients between 2008 and 2017 is demonstrated in Table 2. Age 80+ (HR = 4.042, 95% CI 1.732–9.433, p = 0.001), followed by age 60–79 (HR = 2.296, 95% CI 1.01–5.216, p = 0.047); Gastric primary location (HR = 3.261, 95% CI 1.658–6.417, p = 0.001); Primary GI melanoma with distant metastases (HR = 2.967, 95% CI 2.22–3.965, p = 0); Nonmetropolitan counties not adjacent to a metropolitan area (HR = 2.211, 95% CI 1.253-3.9, p = 0.006); and chemotherapy (HR = 1.417, 95% CI 1.078–1.863, p = 0.012) have the highest overall mortality. The highest cancer specific mortality, was observed in age 80+ (HR = 3.343 ,95% CI 1.424–7.844, p = 0.006); primary gastric location (HR = 3.108, 95% CI 1.518–6.367, p = 0.002), followed by colon (HR = 0.221, 95% CI 0.55–0.895, p = 0.055); advanced disease with distant metastasis (HR = 3.309, 95% CI 2.421–4.522, p = 0), followed by regional lymph node involvement (HR = 1.632, 95% CI 1.058–2.516, p = 0.027); Nonmetropolitan counties not adjacent to a metropolitan area (HR = 2.376, 95% CI 1.344-4.2, p = 0.003); and chemotherapy (HR = 1.45, 95% CI 1.09–1.928, p = 0.11).

Table 2
Crude analysis of factors associated with all-cause mortality and Primary Gastrointestinal Melanoma related mortality among US patients between 2008 and 2017.

Characteristics	Overall Mortality. Crude Proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Crude Proportional Hazard ratio (95% confidence interval)
Age, y.o		
0–39	1.00 (reference)	1.00 (reference)
40–59	1.983(0.857–4.588)	1.822 (0.786–4.223)
60–79	2.296(1.01–5.216) **	2 (0.879–4.553) *
80+	4.042(1.732–9.433) ***	3.343 (1.424–7.844) ***
Race		
Non-Hispanic white	1.00 (reference)	1.00 (reference)
Non-Hispanic black	1.006 (0.585–1.731)	0.86 (0.468–1.582)
Hispanic	1.017(0.738–1.403)	0.961(0.682–1.354)
Other	0.814(0.524–1.266)	0.807(0.509–1.282)
Cancer Site		
Anus	1.00 (reference)	1.00 (reference)
colon	0.5 (0.205–1.22)	0.221(0.55–0.895) **
Esophagus	1.642(0.964–2.795) *	1.662(0.958–2.885) *
Stomach	3.261(1.658–6.417) ***	3.108(1.518–6.367) ***
Rectum	1.128(0.867–1.467)	1.118(0.849–1.472)

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$

Characteristics	Overall Mortality. Crude Proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Crude Proportional Hazard ratio (95% confidence interval)
Small intestine	0.654(0.333–1.284)	0.639(0.313–1.307)
Other	1.462(0.539–3.966)	1.215(0.385–3.834)
Histologic Subtype		
Malignant Melanoma, Not otherwise specified	1.00 (reference)	1.00 (reference)
Nodular melanoma	0.986(0.653–1.489)	0.966(0.623–1.498)
Spindle cell melanoma, Not otherwise specified	0.379(0.094–1.525)	0.428(0.106–1.723)
Mucosal lentiginous melanoma	0.508(0.163–1.59)	0.574(0.183–1.795)
Other	0.375(0.12–1.171) *	0.423(0.135–1.323)
Tumor stage		
Localized	1.00 (reference)	1.00 (reference)
Regional by direct extension only	0.968(0.547–1.715)	1.086(0.596–1.977)
Regional lymph nodes involved only	1.482(0.986–2.225) *	1.632(1.058–2.516) **
Regional by both direct extension and lymph node involvement	1.374(0.873–2.164)	1.587(0.989–2.546) *
Distant	2.967(2.22–3.965) ***	3.309(2.421–4.522) ***
Living area		
Counties in metropolitan areas of 1 million persons	1.00 (reference)	1.00 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	1.014(0.742–1.386)	0.954(0.683–1.333)

*** p < 0.01, ** p < 0.05, * p < 0.1

Characteristics	Overall Mortality. Crude Proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Crude Proportional Hazard ratio (95% confidence interval)
Counties in metropolitan areas of 250,000 persons	0.866(0.539–1.39)	0.895(0.549–1.457)
Nonmetropolitan counties adjacent to a metropolitan area	1.091(0.693–1.718)	0.964(0.584–1.592)
Nonmetropolitan counties not adjacent to a metropolitan area	2.211(1.253-3.9) ***	2.376(1.344-4.2) ***
Income per year		
$< $35,000	1.00 (reference)	1.00 (reference)
$35,000–44,999	1.005(0.38–2.656)	1.206(0.414–3.515)
$45,000–54,999	0.725(0.289–1.824)	0.842(0.302–2.345)
$55,000–64,999	0.634(0.254–1.581)	0.709(0.256–1.962)
$65,000–74,999	0.617(0.248–1.535)	0. 697(0.252–1.925)
$75,000+	0.555(0.224–1.371)	0.643(0.235–1.763)
Marital Status		
Married	1.00 (reference)	1.00 (reference)
Single	0.994(0.691–1.43)	1.029(0.707–1.497)
Divorced/separated	1.011(0.634–1.612)	0.78(0.45–1.352)
Widowed	1.074(0.788–1.465)	1.071(0.773–1.483)
Surgery and Radiation		
No	1.00 (reference)	1.00 (reference)
Yes	0.796 (0.574–1.102)	0.78 (0.552–1.102)

*** p < 0.01, ** p < 0.05, * p < 0.1

Characteristics	Overall Mortality. Crude Proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Crude Proportional Hazard ratio (95% confidence interval)
Chemotherapy		
No	1.00 (reference)	1.00 (reference)
Yes	1.417(1.078–1.863) **	1.45(1.09–1.928) **
Year of diagnosis		
2008	1.00 (reference)	1.00 (reference)
2009	1.308(0.804–2.127)	1.416(0.843–2.378)
2010	1.289(0.76–2.189)	1.347(0.764–2.375)
2011	1.175(0.672–2.051)	1.214(0.665–2.213)
2012	1.006(0.589–1.719)	1.093(0.619–1.929)
2013	1.101(0.645–1.88)	1.238(0.705–2.174)
2014	1.018(0.615–1.685)	1.082(0.632–1.854)
2015	0.856(0.509–1.439)	0.828(0.471–1.456)
2016	0.888(0.5-1.579)	1.017(0.56–1.846)
2017	0.764(0.418–1.399)	0.722(0.374–1.395)
*** p < 0.01, ** p < 0.05, * p < 0.1		

Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and Primary Gastrointestinal Melanoma related mortality among US patients between 2008 and 2017 are demonstrated in Table 3. Higher overall mortality was observed in age 80+ (HR = 5.653, 95% CI 2.212–14.445, p = 0), followed by age 60–79 (HR = 3.062, 95% CI 1.26–7.442, p = 0.014); gastric location of melanoma (HR = 2.821, 95% CI 1.265–6.292, p = 0.011); advanced disease with distant metastasis (HR = 4.491, 95% CI 3.115–6.476, p = 0), followed by regional involvement by both direct extension and lymph node involvement (HR = 1.755, 95% CI 1.047–2.943, p = 0.033). Age 80+ (HR = 4.654, 95% CI 1.79-12.104,

p = 0.002), followed by age 60–79 (HR = 2.815, 95% CI 1.149–6.898, p = 0.024); primary gastric location (HR = 3.05, 95% CI 1.307–7.119, p = 0.01); advanced disease with distant metastases (HR = 5.091, 95% CI 3.424–7.568, p = 0), followed by regional involvement by both direct extension and lymph node involvement (HR = 2.023, 95% CI 1.177–3.479, p = 0.011) have the highest cancer specific mortality.

Table 3
Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and Primary Gastrointestinal Melanoma related mortality among US patients between 2008 and 2017.

Characteristics	Overall Mortality. Adjusted proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Adjusted proportional Hazard ratio (95% confidence interval)
Gender		
Male	1.00 (reference)	1.00 (reference)
Female	1.345(0.99–1.828) *	1.164(0.841–1.609)
Age, y.o		
0–39	1.00 (reference)	1.00 (reference)
40–59	2.612(1.05–6.495) **	2.495(0.996–6.251) *
60–79	3.062(1.26–7.442) **	2.815(1.149–6.898) **
80+	5.653(2.212–14.445) ***	4.654(1.79-12.104) ***
Race		
Non-Hispanic white	1.00 (reference)	1.00 (reference)
Non-Hispanic black	0.79(0.418–1.49)	0.625(0.306–1.275)
Hispanic	0.988(0.677–1.442)	0.949(0.635–1.418)
Other	0.926(0.567–1.514)	0.912(0.546–1.524)
Cancer Site		
Anus	1.00 (reference)	1.00 (reference)
colon	0.489(0.187–1.283)	0.23(0.054–0.979) **
Esophagus	1.376(0.736–2.57)	1.315(0.686–2.521)
Stomach	2.821(1.265–6.292) **	3.05(1.307–7.119) ***
Rectum	1.039(0.768–1.405)	1.012(0.738–1.388)
Small intestine	0.383(0.173–0.846) **	0.375(0.163–0.864) **
Other	0.81(0.267–2.452)	0.627(0.179-2.2)
Histologic Subtype		
Malignant Melanoma, Not otherwise specified	1.00 (reference)	1.00 (reference)

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$

Characteristics	Overall Mortality. Adjusted proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Adjusted proportional Hazard ratio (95% confidence interval)
Nodular melanoma	1.011(0.627–1.632)	0.94(0.564–1.569)
Spindle cell melanoma, Not otherwise specified	0.404(0.091–1.802)	0.4(0.088–1.811)
Mucosal lentiginous melanoma	0.529(0.158–1.772)	0.577(0.171–1.951)
Other	0.364(0.106–1.248)	0.443(0.129–1.523)
Tumor stage		
Localized	1.00 (reference)	1.00 (reference)
Regional by direct extension only	1.1(0.577–2.097)	1.232(0.623–2.437)
Regional lymph nodes involved only	1.664(1.051–2.635) **	1.86(1.139–3.037) **
Regional by both direct extension and lymph node involvement	1.755(1.047–2.943) **	2.023(1.177–3.479) **
Distant	4.491(3.115–6.476) ***	5.091(3.424–7.568) ***
Living area		
Counties in metropolitan areas of 1 million persons	1.00 (reference)	1.00 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	1.114(0.762–1.629)	1.028(0.685–1.541)
Counties in metropolitan areas of 250,000 persons	0.652(0.351–1.209)	0.668(0.353–1.263)
Nonmetropolitan counties adjacent to a metropolitan area	1.28(0.67–2.446)	1.126(0.555–2.284)
Nonmetropolitan counties not adjacent to a metropolitan area	1.067(0.504–2.259)	1.069(0.494–2.315)
Income per year		
$< $35,000	1.00 (reference)	1.00 (reference)
$35,000–44,999	1.248(0.414–3.761)	1.639(0.493–5.445)
$45,000–54,999	0.777(0.272–2.216)	0.932(0.296–2.942)

*** p < 0.01, ** p < 0.05, * p < 0.1

Characteristics	Overall Mortality. Adjusted proportional Hazard ratio (95% confidence interval)	Primary GI melanoma mortality. Adjusted proportional Hazard ratio (95% confidence interval)
$55,000–64,999	0.558(0.188–1.66)	0.664(0.2–2.2)
$65,000–74,999	0.597(0.197–1.81)	0.74(0.219-2.5)
$75,000+	0.465(0.153–1.416)	0.551(0.162–1.872)
Marital Status		
Married	1.00 (reference)	1.00 (reference)
Single	1.116(0.732–1.703)	1.114(0.717–1.731)
Divorced/separated	0.928(0.539–1.598)	0.658(0.35–1.24)
Widowed	1.047(0.718–1.527)	1.024(0.69–1.52)
Surgery and Radiation		
No	1.00 (reference)	1.00 (reference)
Yes	0.943(0.645–1.38)	0.939(0.628–1.402)
Chemotherapy		
No	1.00 (reference)	1.00 (reference)
Yes	0.908(0.645–1.277)	0.852(0.596–1.217)
Year of diagnosis		
2008	1.00 (reference)	1.00 (reference)
2009	1.131(0.626–2.043)	1.147(0.614–2.143)
2010	1.71(0.901–3.244)	1.673(0.849–3.297)
2011	0.866(0.426–1.761)	0.722(0.336–1.55)
2012	0.94(0.488–1.812)	0.939(0.467–1.887)
2013	1.097(0.571–2.106)	1.181(0.597–2.335)
2014	0.837(0.44–1.59)	0.79(0.399–1.563)
2015	0.786(0.422–1.463)	0.718(0.368–1.402)
2016	0.657(0.326–1.326)	0.643(0.31–1.334)
2017	0.785(0.388–1.588)	0.645(0.299–1.392)
*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$		

4. Discussion

Primary non cutaneous melanomas are rare. Only 20% of them arise from mucosal sites and of these, 25% are found in the GI tract [13]. Primary GI melanomas have been associated with poor prognosis and aggressive behavior [11]. However, given its rare occurrence, only a few adequately powered studies have addressed the epidemiology and prognosis factors [11, 14, 15].

Primary gastric location was associated with the highest overall mortality and cancer specific mortality in our cohort. Similar results were found in the Zheng series [11]. However, overall mortality of gastric location, in the multivariate was higher (HR = 2.821, 95% CI 1.265–6.292, p = 0.011) in our cohort compared to the Zheng study (HR = 2.47, 95% CI 1.73–3.50, p = 0.000) [11]. Small intestine location has the lowest overall mortality in our cohort compared to other locations. This finding differs from the Zheng series in which the anal and colonic melanoma had the better overall survival than other GI melanoma subtypes [11].

Our study revealed a male gender predominance, which differed from the zheng series and the Al-Haseni series, which found a higher proportion of females [11, 14]. Most patients were diagnosed between the ages of 60–79 (52.88%), a similar trend was observed in the Zheng series (48.9%). The rectum and the anus were the most common primary sites, consistent with the literature [11, 14, 15]. Populated areas and higher income were associated with higher diagnosis in our cohort. This could be explained by nonspecific symptoms of primary GI melanoma and the need for advanced and costly diagnostic imaging [16–17]. Patients living in populated metropolitan areas have more access to advanced imaging and healthcare services, and patients with higher income are more likely to afford the diagnostic means.

Several epidemiologic cancer studies have found marital status to be an independent prognostic factor. Married patients were found to have a lower overall and cancer specific mortality, compared to their non married counterparts [18–27]. This was mainly thought to be due to better social support among married patients. However, in our cohort, marital status did not significantly impact the overall mortality or cancer specific mortality.

Age 80 + and primary GI melanoma with distant metastases are also associated with higher overall mortality in the univariate analysis. Similar findings are seen in the literature [11]. Interestingly, as noted in our univariate analysis, the same variables i.e., age 80 + and advanced disease with distant metastasis were also associated with higher overall and cancer-specific mortality in our multivariate regression analysis. Elderly patients usually have immunosenescence and/or other associated comorbidities which decreases their ability to fight off the cancer cells [1–3]. Furthermore, primary GI melanomas with distant metastasis are diagnosed very late and not many novel therapies are available currently to target such an advanced cancer, and hence may be associated with poor prognosis as evidenced in our study. Intuitively, it makes sense to assume that in patients who have early detection of their cancer could possibly have a better overall as well as a cancer specific survival outcome associated with a good prognosis. However, to conclusively state that, further larger cohort studies are warranted. Our study sets the stage for future larger studies on the subject to evaluate whether more stringent monitoring could possibly lead to

detection of these primary GI melanomas at an early stage and how early detection affects overall as well as the cancer specific mortality.

Additionally, nonmetropolitan counties not adjacent to a metropolitan area and chemotherapy also have higher overall mortality as noted in our univariate analysis. The patients residing in non-metropolitan counties may not have access to higher tertiary care centers and advanced healthcare facilities in close vicinity which significantly decreases the ability to maintain a regular follow up. Other financial factors as well as sub-optimal healthcare delivery could also be playing a role. However, in the multivariate regression, chemotherapy and residential areas did not yield a higher overall or cancer specific mortality. Also, Surgical resection of primary tumors was associated with lower mortality in the zheng series [11]. However, in our cohort, there was no statistically significant difference between surgical resection and non-surgical resection.

Certain limitations must be considered when interpreting the results of this study. Our study was mainly carried out on primary GI melanoma, this makes it difficult to generalize our results to metastatic GI melanomas. Information gathered on patients that underwent radiotherapy was not complete. Furthermore, the SEER database publicly available does not provide information on comorbidities. However, this study has the merit of collecting data from the largest cancer database in the USA. Furthermore, we were also able to enroll an adequate sample size despite the rarity of the pathology.

5. Conclusion

There is paucity of prior literature on primary GI melanomas, owing to the rarity of the condition. It is associated with aggressive behavior and poor prognosis. Our cohort focused on a 10-year period and demonstrated that advanced age, distant metastasis at diagnosis, and primary location are independent prognosis factors in regard to overall and cancer specific mortality in primary GI melanomas. Surgical resection of primary tumor and marital status was not of prognostic value. This study lays the ground for further prospective studies identifying individuals at an increased risk of primary GI melanomas, earlier and closer screenings in such individuals.

List Of Abbreviations

Gastrointestinal: GI

Surveillance, Epidemiology, and End Results: SEER

Overall mortality: OM

cancer-specific mortality: CSM

Hazard ratio: HR

United States National Cancer Institute: US NCI

Confidence Interval: CI

Declarations

Ethics approval and consent for publication:

The SEER Dataset was a public-use dataset, of which the informed consent was waived.

Availability of data and materials:

The data used and/or analyzed in this study are available in the Surveillance, Epidemiology, and End Results (SEER) Database of the National Cancer Institute (http://seer.cancer.gov).

Competing interests/ conflicts of interest:

Not applicable.

Funding:

Not applicable.

Authors' contributions:

Ayrton Bangolo searched the literature, wrote, and revised the manuscript. Pierre Fwelo extracted and analysed the data, revised, and edited the manuscript. John Bukasa, Chinmay Trivedi, Mohamed Ahmed, Trupti Waykole and Jennifer Hashem revised and edited the manuscript. Tracy Proverbs-Singh and Sameh Elias revised and approved the final version and are the article's guarantors. All authors certify that they contributed sufficiently to the intellectual content and data analysis. Each author has reviewed the final version of the manuscript and approves it for publication.

Acknowledgement:

Not applicable.

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