SUBMITTED 4 SEP 23
REVISION REQ. 26 OCT 23; REVISION RECD. 25 NOV 23
ACCEPTED 26 DEC 23
ONLINE-FIRST: MARCH 2023
DOI: https://doi.org/10.18295/squmj.3.2024.015

Clinicopathological Features and Outcomes of Endometrial Cancer

A single institution experience

***Ikram A. Burney,[1] Shahd Al Ghafri,[2] Jawahar Al Noumani,[3] Anisa Al Jabri,[4] Anjum O. Hasan,[1] Sarya Bella,[1] Hasan K. AlSayegh,[5] Radhiya Al Ajmi,[6] Moza Al Kalbani[1]**

[1]Women Health Program, Sultan Qaboos Comprehensive Cancer Care and Research Center, Muscat, Oman; Departments of [2]Surgery and [4]Radiation Oncology, The Royal Hospital, Muscat, Oman; Departments of [3]Medicine and [6]Pathology, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman; [5]Department of Research Laboratories, Sultan Qaboos Comprehensive Cancer Care and Research Center, Muscat, Oman.

**Corresponding Author's e-mail: i.burney@cccrc.gov.om; ikramburney@hotmail.com*

Abstract

Objective: Endometrial cancer (EC) is the 6th most common cancer in women worldwide, and the 5th most common cancer in women in Oman. Survival outcomes of EC have not been reported previously from Oman. We report the demographic features, clinical presentation, pathological types, and long-term outcomes of patients diagnosed with EC in Oman. ***Methods:*** A retrospective analysis was carried out on consecutive patients treated at a single tertiary referral center in Oman. Survival was estimated using the method of Kaplan and Meier. ***Results:*** A total of 50 consecutive patients with EC were included. Median age was 61 years (range 31-86 years), 72% had type I histology. Most patients were diagnosed to have stage IA and IB (49% and 20%) respectively, and the majority of patients had grade 1 or 2 tumors (40% and 34%) respectively. Overall, the 5-year survival was estimated to be 70%, and the 10-year survival rate was 56%. Weight (> 75 kg) and BMI (>30kg/m^2) were significantly associated with a better survival.

Tumor histology (Type I *vs* Type II or carcinosarcoma), grade (1 *vs* 2 *vs* 3), and stage (IA or IB *vs* II-IV) were associated with better overall survival (p=0.007, <0.0001, and <0.0003 respectively). Patients with EC with co-morbidities, other than obesity, had inferior survival compared to those who did not had co-morbidities. ***Conclusion:*** Median age at presentation, histological sub-type, clinical stage, and outcomes are comparable to the published literature. Almost two-thirds of the patients were obese. These data could be used as a benchmark for outcomes of EC in the region.

Keywords: Endometrial Cancer; Endometroid type, obesity and cancer; Oman.

Advances in Knowledge:

- In Oman, the outcomes of patients diagnosed to have endometrial cancer are comparable to the published literature from the region and internationally.
- Almost 2/3rd of the patients are obese at the time of diagnosis
- Patients who are overweight and obese have better prognosis, as the vast majority have endometroid type of endometrial cancer

Application to patient care:

- Around 50% of the patient are diagnosed to have stage I disease at presentation, and surgical treatment suffices
- All other patients require adjuvant radiotherapy, chemotherapy, both, or palliative treatment.
- These data presented in this paper could be used as a benchmark for outcomes of EC in the region

Introduction

Endometrial cancer (EC) is the 6th most common cancer in women worldwide, with an incidence of 10.1 per 100, 000 and a mortality rate of 2.4 per 100 000 patients.[1] Incidence rates vary in different parts of the world, EC being the commonest gynecological cancer in the western world.[2,3] In the last two decades, an increase in incidence of EC has been reported, possibly related to the rising prevalence of obesity. Obesity my increase the risk of endometrial cancer by 2.6 folds, and with severe obesity, the risk increases by 4.6 folds.[4] There are several other risk

factors which predispose to EC, and these are classifiable into 2 groups: Modifiable risk factors include pelvic radiation therapy, duration of menstruation, late menopause, early menstruation, diabetes, fatty diet, polycystic ovarian disease, supplements, tamoxifen, pregnancy, and endometrial hyperplasia. Non-modifiable risk factors include age & family history. Family history of EC increases the risk by 2-3 folds.[5]

EC is of 2 major sub-types; type I or endometroid adenocarcinoma accounts for around 80% of all EC, and type II carcinoma accounts for 15-20%, including serous carcinoma, clear cell carcinoma, and carcinosarcoma.[6] Type I EC are usually estrogen-receptor positive, present with localized disease, and have a favorable prognosis, whereas, type II EC usually do not express estrogen-receptor, present with advanced stage disease, and have a poor prognosis.[7] Five-year survival amongst patients with metastatic disease has been reported to be around 17%.[8] More recently, EC has been classified according to the molecular profile. Subtypes include; POLE-ultra mutated (POLEmut) has the best prognosis, mismatch repair–deficient (MMRd), and no specific molecular profile (NSMP) EC, both have an intermediate prognosis, and p53-abnormal (p53abn) which has the worst prognosis.[9]

EC is the 5th most common cancer in women in Oman, after breast, thyroid, colorectal and stomach cancers.[10] There is a geographical variation in the incidence and presentation of EC worldwide. For example, mutation frequency profile for different ethnicities and tumor grades in endometrial cancer patients revealed a higher mutation frequency for PIK3CA and ARID1A in White and Asian patients; TP53 and FAT1 in Black/African Americans; and CTNNB1 and RYR2 in Native Hawaiians or Asians.[11] Also, important variations in incidence and mortality rates of EC have been reported over the last 3 decades.[12] Hence it is important to report the presenting features and outcomes of EC patients in Oman and the region. We aimed to report the demographic features, clinical presentation, pathological types, and long-term outcomes of patients with EC in Oman.

Methods

Study population and variables:

Consecutive patients diagnosed to have EC and treated at the Sultan Qaboos University Hospital (SQUH), Muscat, Oman, were the subjects of this analysis. SQUH was one of the two referral centers for cancer treatment in Oman. Patients diagnosed to have uterine sarcoma, lymphoma, or metastatic disease were excluded. Electronic patient records (EPR) of patients diagnosed with EC between 2008 and 2020 were reviewed and demographic features including age and co-morbid illnesses were extracted. Body mass index was calculated using the height and weight at the time of diagnosis. A patient was defined to have diabetes, hypertension, or ischemic heart disease (IHD) or hyperlipidemia, if the illness had been noted in the EPR, or the patient was receiving treatment for those conditions at the time of diagnosis. Information on histological sub-type and tumor grade was extracted from the archived notes and verified by a single pathologist. Overall survival outcomes were measured from the date of diagnosis to the date of death for deceased patients or date of last follow-up (on or before Dec 31, 2021) for censored patients. The study was approved by the institutional Medical Research Ethics Committee.

Statistics:

Median and range were reported for the continuous variables; frequency and proportions were reported for the categorical variables. Five-year overall survival (OS) estimates was calculated using the Kaplan-Meier method.[13] Comparisons of study groups were performed using the log-rank test. A p-value ≤ 0.05 was considered statistically significant. Analysis was performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Over the study period, a total of 50 patients were diagnosed to have EC, and all were included in the analysis. Baseline characteristics are shown in Table 1. Median age was 61 years (range= 31-86 years). Median weight was 76 kg (range=34-126 kg). Mean BMI was 34 kg/m^2, and 62% patients were obese (BMI more than 30 kg/m^2). Thirty-six (72%) patients had type I tumors. Four (8%) patients were diagnosed to have carcinosarcoma. Most patients presented with stage IA and IB disease (49% and 20% respectively), and most patients had grade 1 and 2 tumors (40% and 34% respectively). Thirteen patients died during the follow-up time with a median

time from diagnosis to death of 2 years (range= 4 months – 5.8 years); 37 survived to the last follow-up with median follow-up time of 3.4 years. Overall survival was 70% (±8%) at 5 years and 56% (±11%) at 10 years from diagnosis.

Table 2 & figures 1-4 show overall survival outcomes. Patients who weighed more than75 kg at diagnosis had a 92% (±7%) overall survival rate at four years compared to 48% (±12%) for patient whose weight was less than 75 kg (p=0.001). Twenty-eight patients were obese (had a BMI more than 30 kg/m^2), and had a better 5-year survival compared to those whose BMI was less than 30 kg/m^2 (89% vs 52%; p=0.009). The overall survival outcomes were also significantly associated with the tumor histology (p=0.007), grade p (< 0.0001), and stage I vs II-IV (p <0.0003). History of ischemic heart disease was associated with a statistically significant worse survival. Patients with IHD (n=4) had overall survival of 50% (±25%) at 2 years and 0% at 5 years from diagnosis compared to 89% (±5%) and 74% (±8%) for patients without IHD (n=45).

Discussion

This is the first study reporting the demographic, pathological and clinical features at presentation and outcomes after treatment of EC from Oman. EC is one of the most common cancer, and the most common gynecological cancer in the Gulf Cooperation Council (GCC) region and globally. Data are available from tumor registries from several member states of the GCC.[10] However, these data are limited, because they report the incidence, the location of the patients, the age, and the histological sub-types.[10] There are no studies on the presenting features, presence of co-morbidities, clinical stage, and long-term survival of patients from the GCC. However, a few studies from Turkey and Saudi Arabia have been reported.[14,15] The median age of patients at diagnosis with EC was 61 years, which compares well with the registry data from the Kingdom of Saudi Arabia (60 years), and also with reports from the Western literature (50-70 years).[16,17]

Almost 2/3rd of the patients were obese. This result is in conformity with the studies published from United States which reported that 72% of the patients were either overweight or obese.[18] Obesity is an important modifiable risk factor in endometrial cancer, and cancers of the gall

bladder, esophagus and kidney, and post-menopausal breast.[19,20] In our cohort, obese patients had a significantly better survival than patients with a BMI of less than 30kg/m^2. The relationship between obesity and mortality in patients with EC has been a subject of debate. On the one hand, every 5kg/m^2 increase in BMI has been shown to confer an increased risk of EC, however, obesity-driven ECs are usually type I, low grade, and are diagnosed at an early stage.[18] On the other hand, obesity predisposes to a range of co-morbidities, including diabetes mellitus, hypertension, and ischemic heart disease. Women with BMI of more than 35kg/m^2 have been reported to have an almost 5-fold higher risk of cardiovascular-related mortality 10 years after diagnosis of EC.[21] Women with BMI ≥40kg/m2 had significantly higher odds of all-cause mortality. There are no consistent reports of association between diabetes mellitus and EC related mortality.[22,23] Furthermore, obesity may affect the safe and effective delivery of treatment. For example, obese patients are less likely to be offered hysterectomy, may receive sub-optimal doses of radiotherapy and chemotherapy.[24] In our cohort, 48%, 38%, 22% and 8% patients had hypertension, diabetes mellitus, dyslipidemia and IHD respectively, however, only patients with ischemic heart disease had a significantly inferior survival compared to those who did not had IHD.

All patients received treatment based on the NCCN guidelines.[25] Based on clinical stage, and pathological and molecular factors, EC can be classified into low risk, intermediate risk, high-intermediate risk, high-risk, and advanced metastatic disease.[26] Low risk endometrial cancer doesn't need to be treated with adjuvant treatment after surgery. The role of adjuvant chemotherapy is controversial in EC.[27,28] Despite the fact that early stage EC has better prognosis, 5-30% of cases experience distant metastasis. More than 70 % of type II EC develop distant metastasis. Adjuvant chemotherapy does not improve 5-year overall survival, for patients with high-risk endometrial cancer, but does increase failure-free survival. Hence, the treatment should be individualized after shared decision making.[29]

There are several limitations of this study. Firstly. the study covered a long period of 12 years. However, the standards of care did not change significantly over the study period, and this factor is unlikely to change the results of the study in terms of survival outcomes. For example, molecular classification was first reported in 2013,[9] but was not used until 2020 in routine

clinical practice, affecting the treatment decisions. Immune checkpoint inhibitors were approved for use in recurrent EC only in 2020.[30] Secondly, the study was retrospective and is subject to biases inherent in retrospective data collection. Thirdly, the sample size was relatively small (n=50), however, results support, and are in conformity with the published studies, both regionally and internationally. Finally, we report experience from a single center, however, patients diagnosed to have cancer in Oman receive the initial treatment in one of the two hospitals, and both are located in the capital, Muscat. The patients are referred either to the Ministry of Health Hospitals, or the University Hospital. Since the patients are received from all over the country in our institution, it would be plausible to think, that the pattern of presentation and outcomes reflect the situation in the country.

Conclusion

Median age at presentation, histological sub-type, clinical stage, and survival outcomes amongst patients with EC in Oman are comparable to the published literature. Histological sub-type, degree of differentiation, and clinical stage, were associated with survival. Almost 2/3rd patients were obese, and had a better overall survival because of good prognostic factor disease. These data could be used as a benchmark for outcomes of EC in the region.

Authors' Contribution

IAB conceptualized and designed the study. IAB and MK managed the project. SG, JN, AOH and SB collected the data. HKS analysed the data. IAB, SG, JN, AJ, AOH and SB drafted the manuscript. IAB, RA and MK reviewed the manuscript. All authors approved the final version of the manuscript.

Acknowledgements

We acknowledge all the patients whose data were included in this manuscript. We also acknowledge all medical and healthcare staff involved in the management of patients, whose data is included in this study.

Conflicts of Interest

The authors declare no conflict of interests.

Funding

No funding was received for this study.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660.
2. Henley SJ, Ward EM, Scott S et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer 2020;126: 2225–2249. 2.
3. Siegel RL, Miller KD, Fuchs HE et al. Cancer statistics, 2021. CA Cancer J Clin 2021; 71:7–33.
4. Raglan O, Kalliala I, Markozannes G, et al. Risk factors for endometrial cancer: An umbrella review of the literature. Int J Cancer. 2019 Oct 1;145(7):1719-1730. doi: 10.1002/ijc.31961.
5. Plotti F, Capriglione S, Scaletta G, et al. Implementing the Risk of Endometrial Malignancy Algorithm (REM) adding obesity as a predictive factor: Results of REM-B in a single-center survey. Eur J Obstet Gynecol Reprod Biol. 2018 Jun;225:51-56. doi: 10.1016/j.ejogrb.2018.03.044.
6. Kitchener HC, Trimble EL; Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. Int J Gynecol Cancer. 2009 Jan;19(1):134-40. doi: 10.1111/IGC.0b013e3181995f90.
7. Setiawan VW, Yang HP, Pike MC, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013 Jul 10;31(20):2607-18. doi: 10.1200/JCO.2012.48.2596.
8. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review 1975- 2017. National Cancer Institute. April 15, 2020 (https://seer.cancer.gov/csr/1975_2017/)
9. Cancer Genome Atlas Research Network; Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013 May 2;497(7447):67-73. doi: 10.1038/nature12113.
10. Cancer Incidence in Oman 2019. www.moh.gov.om/en/web/general-directorate- of-primary-health-care/resources.

11. Althubiti MA. Mutation Frequencies in Endometrial Cancer Patients of Different Ethnicities and Tumor Grades: An Analytical Study. Saudi J Med Med Sci. 2019 Jan-Apr;7(1):16-21. doi: 10.4103/sjmms.sjmms_154_18.
12. Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, Zhang C. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990-2019. Gynecol Oncol. 2021 May;161(2):573-580. doi: 10.1016/j.ygyno.2021.01.036.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Amer Statist Assn. 1958. 53, 457–481.
14. Erkanli S, Eren F, Pekin S, Bagis T. BCL-2 and P53 expression in endometrial carcinoma. J Exp Clin Cancer Res. 2004 Mar;23(1):97-103.
15. Al Asiri M, Tunio MA, Bayoumi Y, et al. Five years treatment outcomes of postoperative radiotherapy in saudi women with uterine cancers: single institutional experience. Gulf J Oncolog. 2014 Jul;1(16):32-9.
16. Al-Kadri HM, Al-Awami SH, Madkhali AM. Assessment of risk factors of uterine cancer in Saudi patients with postmenopausal bleeding. Saudi Med J. 2004 Jul;25(7):857-61.
17. Almohammadi NH. The pattern of gynecological malignancies in Al-Madinah Al-Munawarah region, Saudi Arabia: An overview of 6 years. Saudi Med J. 2022 Mar;43(3):283-290. doi: 10.15537/smj.2022.43.3.20210888.
18. Arem H, Park Y, Pelser C, et al. Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. J Natl Cancer Inst. 2013 Mar 6;105(5):342-9. doi: 10.1093/jnci/djs530.
19. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies, 2008. 371, 569. doi:10.1016/S0140-6736(08)60269-X
20. Njoku K, Barr CE, Crosbie EJ. Current and Emerging Prognostic Biomarkers in Endometrial Cancer. Front Oncol. 2022 Apr 22;12:890908. doi: 10.3389/fonc.2022.890908.
21. Secord AA, Hasselblad V, Von Gruenigen VE, et al. Body mass index and mortality in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol. 2016 Jan;140(1):184-90. doi: 10.1016/j.ygyno.2015.10.020.

22. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer. 2013. Feb;23(2):294-303. doi: 10.1097/IGC.0b013e31827b8430.
23. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is Diabetes Mellitus Associated with Increased Incidence and Disease-Specific Mortality in Endometrial Cancer? A Systematic Review and Meta-Analysis of Cohort Studies. Gynecol Oncol 2014. 135(1):163–71. doi: 10.1016/j.ygyno.2014.07.095
24. Slawinski CGV, Barriuso J, Guo H, Renehan AG. Obesity and Cancer Treatment Outcomes: Interpreting the Complex Evidence. Clin Oncol (R Coll Radiol). 2020 Sep;32(9):591-608. doi: 10.1016/j.clon.2020.05.004.
25. NCCN guidelines for treatment of uterine neoplasms. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473. Accessed on Feb 7, 2023.
26. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. International Journal of Gynecologic Cancer Published Online First: 18 December 2020. doi: 10.1136/ijgc-2020-002230
27. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. Cochrane Database Syst Rev. 2014 May 15;2014(5):CD010681. doi: 10.1002/14651858.CD010681.pub2.
28. Gómez-Raposo C, Merino Salvador M, Aguayo Zamora C, Casado Saenz E. Adjuvant chemotherapy in endometrial cancer. Cancer Chemother Pharmacol. 2020 Mar;85(3):477-486. doi: 10.1007/s00280-019-04027-6.
29. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018 Mar;19(3):295-309. doi: 10.1016/S1470-2045(18)30079-2.
30. Arora S, Balasubramaniam S, Zhang W, et al. FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis. Clin Cancer Res. 2020 Oct 1;26(19):5062-5067. doi: 10.1158/1078-0432.CCR-19-3979.

Table 1: Baseline characteristics of the study population

	Median (range), or Frequency (%)
Age (years)	61 (31-86)
Weight (kg)	76 (34-126)
Height (cm)	152 (131-165)
BMI	34 (15-67)
BMI Category (kg/m^2)	
<18 (underweight)	1 (2%)
18-<24 (normal weight)	6 (13%)
25-<30 (overweight)	10 (22%)
≥30 (obese)	28 (62%)
Histology	
Type I	36 (72%)
Type II	10 (20%)
Carcinosarcoma	4 (8%)
Grade	
Grade 1	20 (40%)
Grade 2	17 (34%)
Grade 3	13 (26%)
Stage	
Stage 1A	24 (49%)
Stage 1B	10 (20.4%)
Stage 2	4 (8.2%)
Stage 3	8 (16.3%)
Stage 4	4 (8.2%)
Hypertension	24 (48%)
Ischemia heart disease	4 (8%)
Hyperlipidemia	11 (22%)
Diabetes Mellites	19 (38%)

Table 2: Four-year overall survival (OS) and standard errors (SE) of the study groups

	N	5-year OS (SE)	Log-rank test p-value*
Age (years)			0.3
<60	21	73% (±12%)	
≥60	29	68% (±10%)	
Weight (kg)			**0.001**
<75	22	48% (±12%)	
≥75	24	92% (±7%)	
Height (cm)			0.4
>150	15	72% (±14%)	
≥150	30	72% (±10%)	
BMI			**0.009**
<30	17	52% (±13%)	
≥30	28	89% (±8%)	
Histology			**0.007**
Type I	36	90% (±5%)	
Type II	10	18% (±16%)	
Type III	4	33% (±27%)	
Grade			**<0.0001**
Grade 1	20	100% (±0%)	
Grade 2	17	78% (±12%)	
Carcinosarcoma	13	0%	
Stage			**<0.0003**
Stage IA/IB	34	90% (±5%)	
Stage II-IV	16	35% (±13%)	
Hypertension			0.14
Yes	24	65% (±11%)	
No	26	74% (±11%)	
Ischemic heart disease			**<0.0001**
Yes	4	0% (NA)	
No	45	74% (±8%)	
Hyperlipidemia			0.7
Yes	11	69% (±15%)	
No	39	70% (±9%)	
Diabetes Mellites			0.2
Yes	19	63% (±12%)	
No	31	74% (±10%)	

**p-values ≤0.05 are statistically significant*

***Abbreviations: OS=overall survival. SE=standard error. NA=not available, value cannot be estimated*

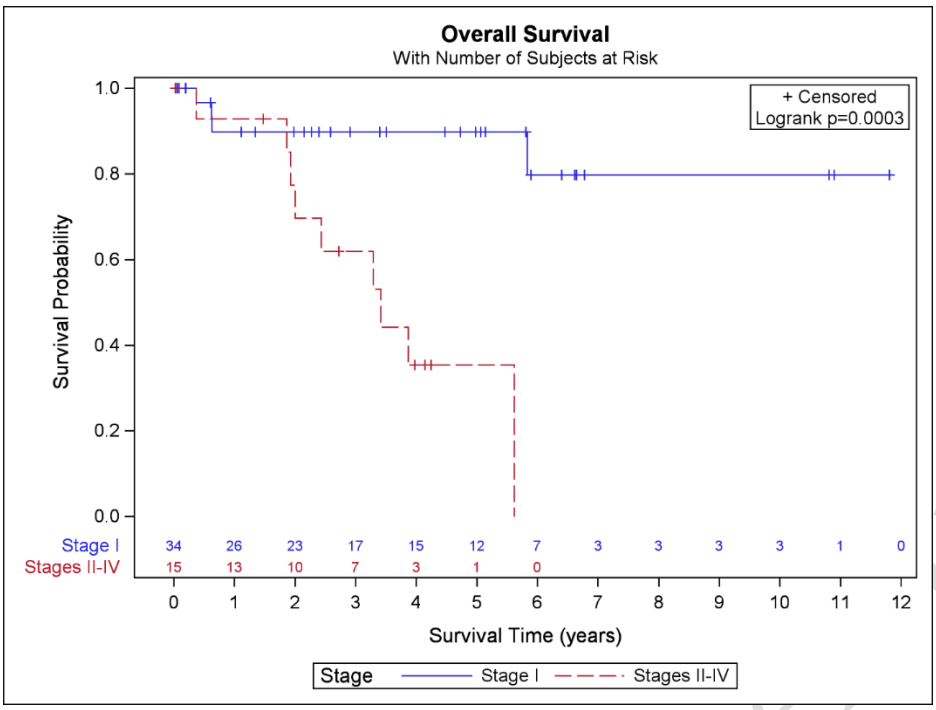

Figure 1A: Overall survival by tumor stage**.**

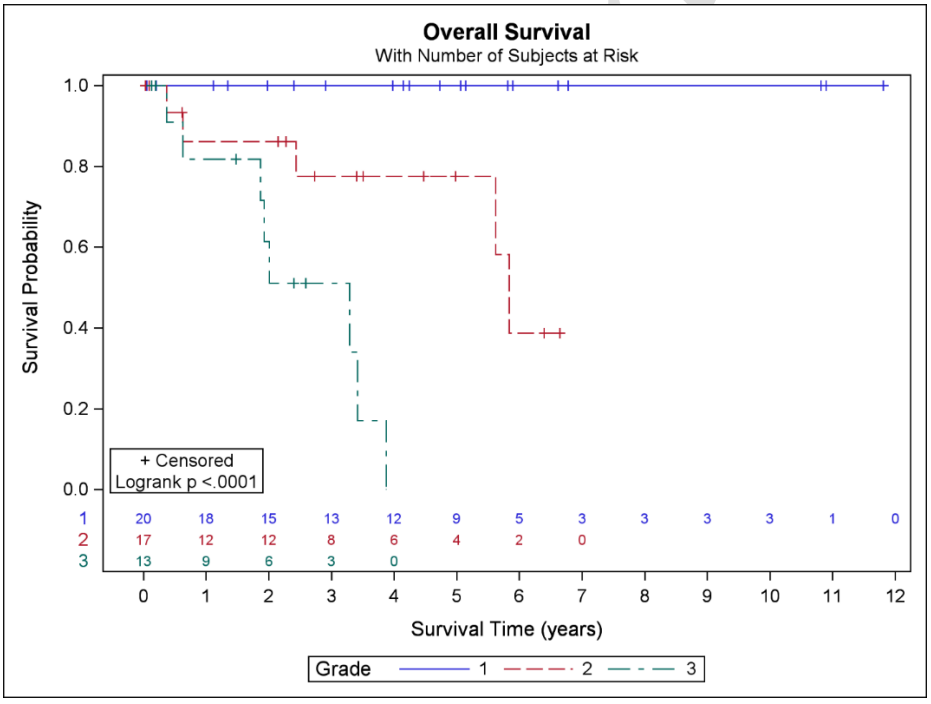

Figure 1B: Overall survival by tumor grade.

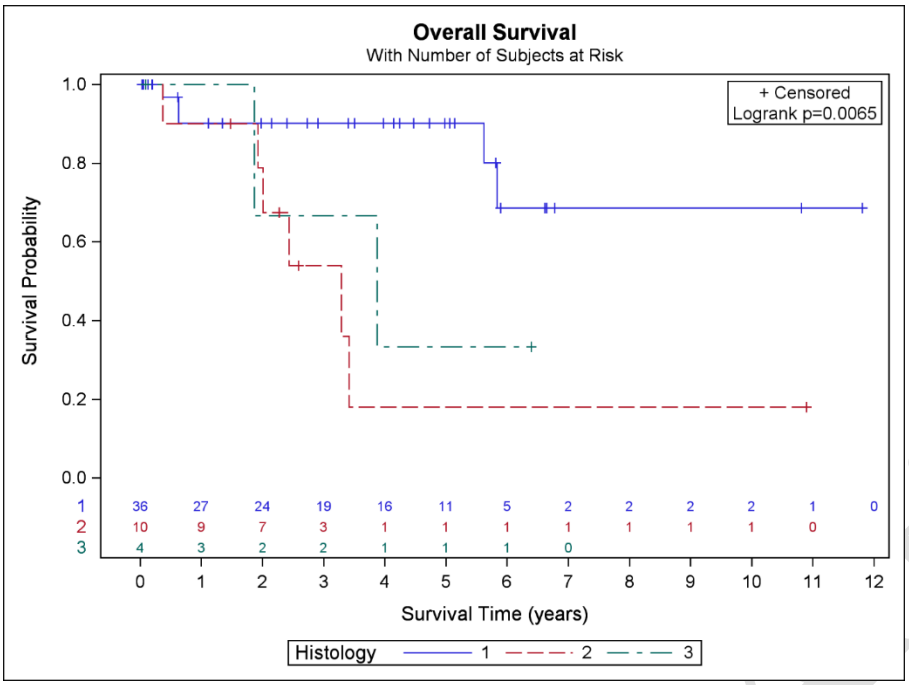

Figure 2: Overall survival by histological type.

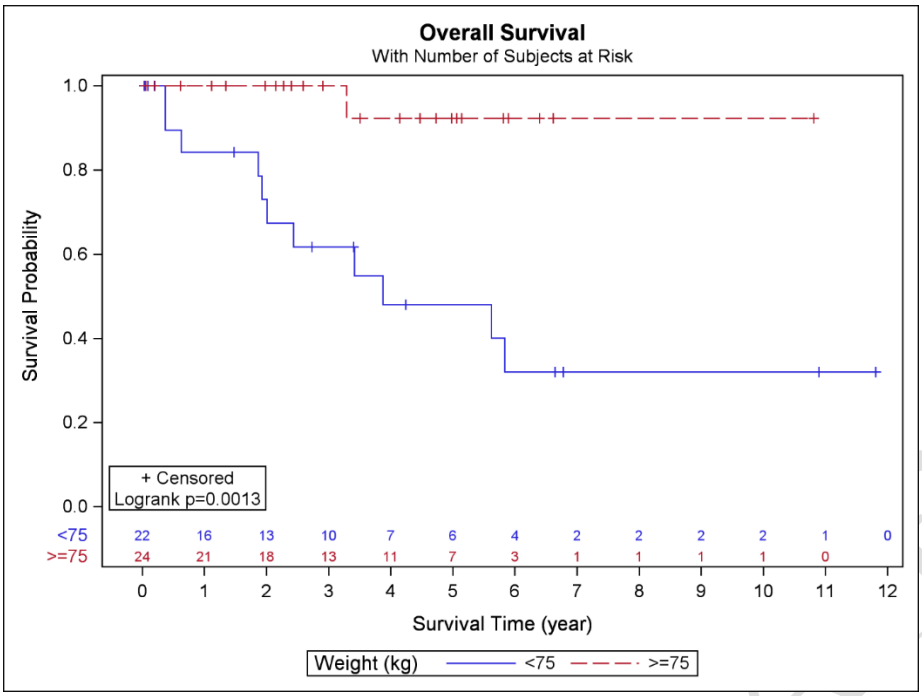

Figure 3A: Overall survival by weight.

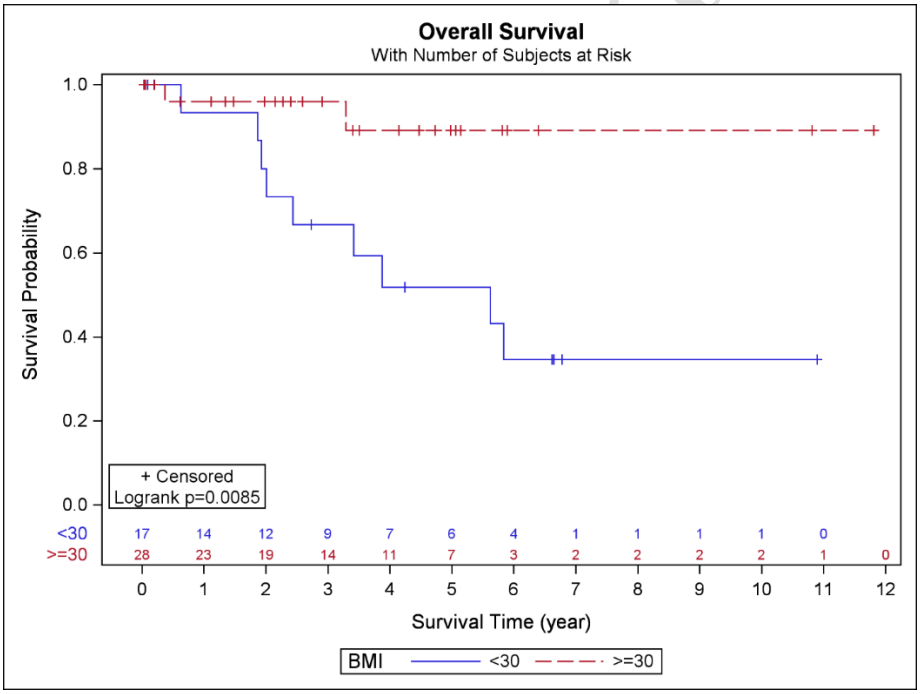

Figure 3B: Overall survival by BMI.

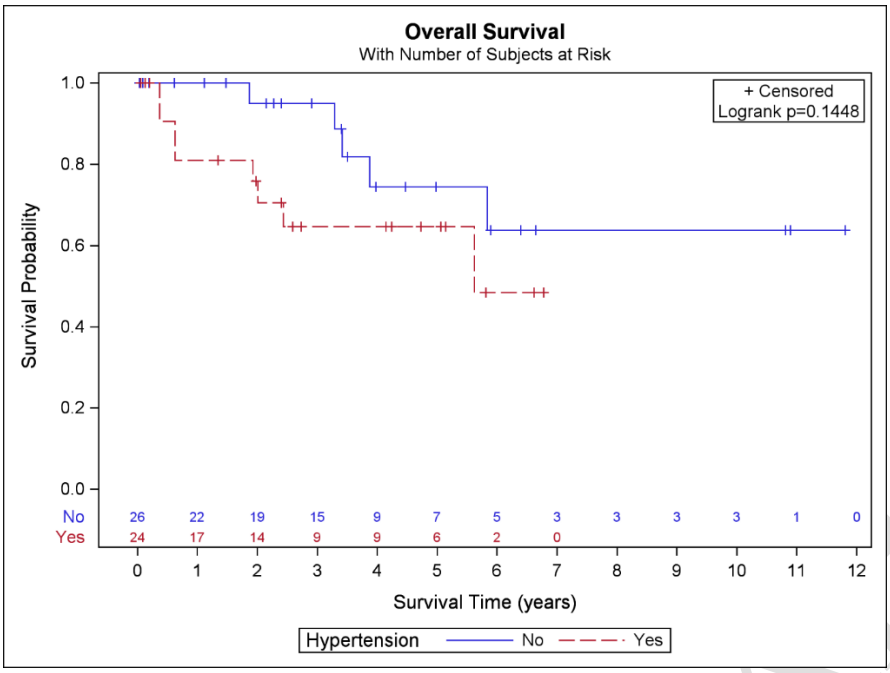

Figure 4A: Overall survival by hypertension.

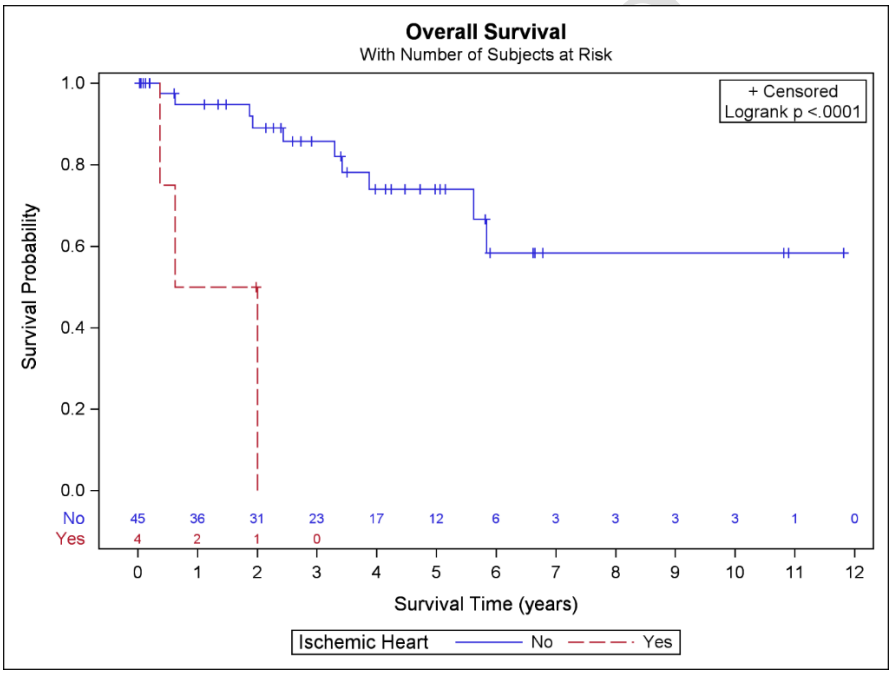

Figure 4B: Overall survival by ischemic heart disease.

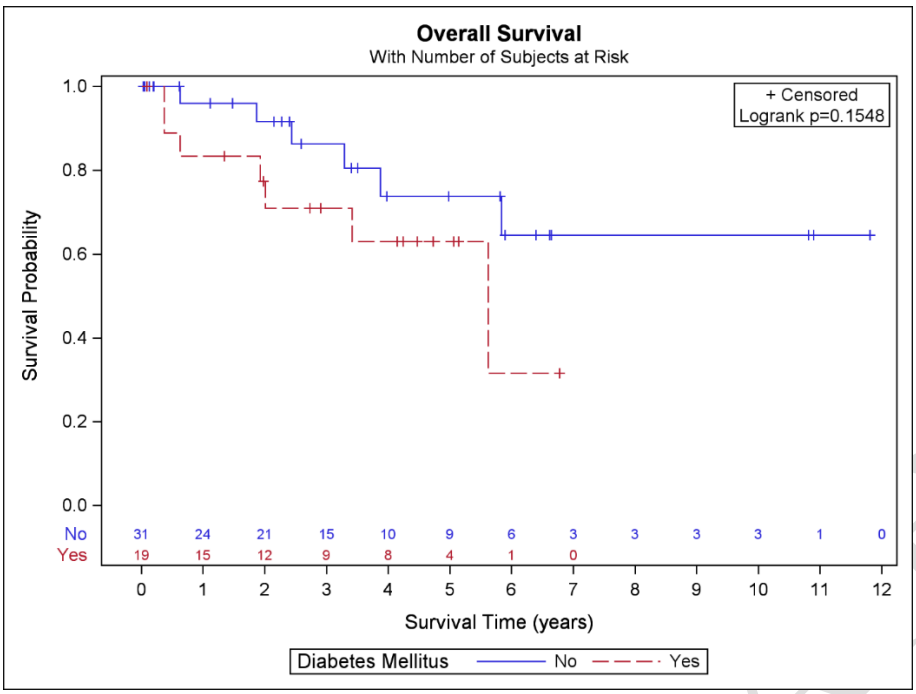

Figure 4C: Overall survival by diabetes mellitus.

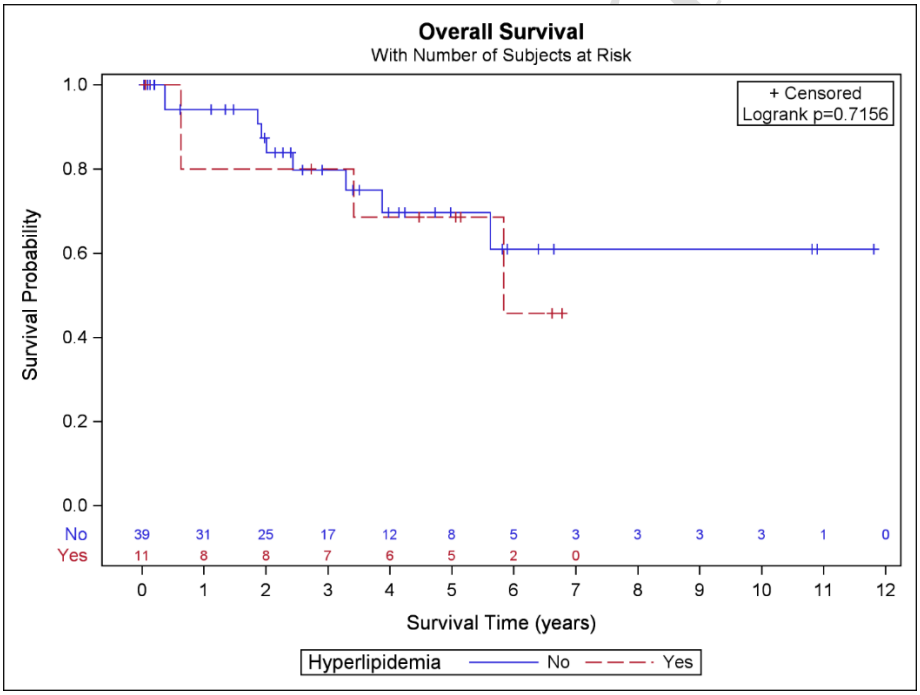

Figure 4D: Overall survival by hyperlipidemia.