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Alcohol Abuse Decreases Pelvic Control and Survival in Cervical Cancer: An Opportunity of Lifestyle Intervention for Outcome Improvement

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Abstract

Purpose—We examined the incidence and effect of alcohol abuse on pelvic control (PC), disease free survival (DFS) and overall survival (OS) in locally advanced cervical cancer patients undergoing definitive radiation (RT).

Methods—Between 2007– 2013, 95 patients treated with RT were reviewed, and the tumor characteristics, RT dose, treatment time, chemotherapy, and number of cycles recorded. The association between alcohol abuse and DFS, OS, and duration of PC was analyzed using multivariable Cox proportional hazards models.

Results—Of the 95 patients with an average age of 54.8 years (range, 27–91 years), 30% were FIGO stage 1B1, 1B2, 2A; 52% stage 2B, 3A; and 18% stage 3B, 86% of the patients were treated with weekly cisplatin chemotherapy. Alcohol history showed that 10 (10.5%) patients met the CDC criteria for heavy alcohol use. With a mean follow up time of 2 years, 85 patients (88.5%) achieved PC and 86 patients (90.5%) were free of distant metastasis. 82 patients (86.3%) were alive at point of last follow up. When controlling for total treatment time, excessive alcohol abuse was significantly associated with a decrease in DFS (p=0.005, HR of 6.19, 95% CI (1.73,22.18)), and OS (p=0.001, HR 6.68, 95% CI (2.10,21.26)) and PC (p=0.029, HR 3.10, 95% CI (1.13,8.56)) on univariable analysis. On multivariable analysis, excessive alcohol abuse was significantly associated with a decrease in DFS (p=0.005, HR 10.57, 95% CI (2.07, 53.93)) and OS (p=0.001, HR 10.80, 95% CI (2.57, 45.40)).

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Conclusion—In this small hypothesis generating series of patients with heavy alcohol use, the data would support the association that heavy alcohol use increases the risk of cancer recurrence and mortality. Additional research is required to define better the patient and treatment related factors which may be targeted for intervention.

Introduction

In 2013, there is an estimated 12,360 patients who will be diagnosed with cervical cancer, and 4,020 deaths due to the disease in the United States [1]. However, in developing countries, cervical cancer remains the number-one cause of cancer related deaths among women, with nearly 500,000 women diagnosed annually world-wide. The use of concurrent chemoradiation therapy has been shown to increase survival and is a global standard of care for locally advanced cervical cancer [2–4]. In a meta-analysis of chemoradiation trials, the addition of chemotherapy to radiation improved 5 year survival from 50% to 58% (12).

Throughout the last decade there continues to be strides to decrease the death rate in patients with locally advanced cervical cancer with the anticipated discovery and use of novel therapeutics in the field. For example, the role of adjuvant chemotherapy after standard chemoradiation has been shown to improve overall survival in a recent phase 3 randomized trial in Mexico [5]. However, intensification of therapy is not without potential significant toxicity; patients on this trial who received adjuvant chemotherapy experienced a higher risk of Grade 3 and 4 toxicity, 86.5% *v* 46.3%, respectively, $P = .001$[5].

Due to the potential for adverse side effects from treatment intensification and the poor disease free survival of locally advanced cervical cancer, there have been increasing efforts to target lifestyle modification to improve outcomes. There is a paucity of data in investigating the role of alcohol consumption and cervical cancer outcomes. In addition, if selected modifications are targeted appropriately, this intervention can impact clinical practice and cancer outcomes as well as improve quality of care in the survivorship period.

Heavy alcohol use causes about 88,000 deaths per year in the United States, which makes excessive alcohol the 3rd leading cause of lifestyle related mortality [6, 7]. There is an average of 30 years of potential life lost for each death due to alcohol [6]. Alcohol use has a major impact on the health system and disease prevention. There were an excess of 2.7 million physician related office visits and 1.2 million emergency room visits in 2006 related to heavy alcohol usage with an estimated cost of $223.5 billion [8]. Alcoholism has health ramifications include the increase risk of developing a variety of cancers, with a potential increased risk of cancer recurrence [9].

The objectives of our study are to evaluate the incidence of heavy alcohol consumption in our locally advanced cervical cancer population and determine the effects of this lifestyle behavior on disease specific survival (DFS), pelvic recurrence, and overall survival (OS).

Methods

Patient Characteristics

Between July 2007 and June 2013, 95 patients received radiation or chemoradiation with brachytherapy for definitive treatment of locally advanced cervical cancer. After obtaining permission from our institutional review board, a retrospective review was conducted to determine alcohol consumption using the center for disease control definition of heavy alcohol consumption being >1 drinks per day on average (CDC http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm). Patient characteristics recorded including age, smoking habits, illicit drug usage, ethnicity, Charleston comorbidity index, Karnofsky Performance Status (KPS). Recorded tumor characteristics included stage and tumor histology. Cervical cancers were staged based on the International Federation of Gynecology and Obstetrics (FIGO) staging system. Cervical histology was based on pathology reports and categorized as squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. Treatment parameters examined included total treatment time of radiation, type of chemotherapy and number of cycles, external beam (EBRT) and brachytherapy radiation dosage, and use of an external beam radiation parametria boost.

Treatment Procedure

The patients were treated with concurrent chemotherapy consisting of weekly cisplatin 40mg/m² or 5-FU 1000mg/m². They received EBRT to the entire pelvis using a 4 field conformal technique. Radiation was delivered in five fractions per week for a total of 45 Gy in 25 fractions, with a parametrial or lymph node boost given depending on the extent of disease, typically consisting of 3 to 5 additional fractions. Patients subsequently underwent intracavitary high-dose-rate (HDR) brachytherapy using a tandem and ring applicator. During brachytherapy, a rectal retractor was placed and the vagina was packed with gauze to minimize applicator movement. Computed tomography (CT) scout images and axial CT images of 3mm slice thickness were obtained once the applicator was in place.

Three-Dimensional (3D) Treatment Planning

For 3D treatment planning following brachytherapy, we used Varian Eclipse BrachyVision (v 8.1). The following reference points were identified: International Commission on Radiation Units and Measurements (ICRU) rectal points and Manchester's A and B points. The ICRU rectal point was defined as the point on the lateral plain film 5mm behind the packing at the level of the tandem ring. A manual optimization was carried out using the planning software with a traditional loading pattern of the tandem and ring. The dose was normalized to point A with the HDR prescription dose of 6 Gy for 5 fractions or 8 Gy for 3 fractions. From 2007 to the beginning of 2011, the brachytherapy prescriptions were normalized to ICRU point A. Since 2011, our current practice is to normalize to ICRU point A and then using CT based imaged guided techniques, manually adjust the dwell times to account for volumetric dose constraints to the high-risk clinical target volume, rectum, sigmoid, and bladder.

Statistical methods

The relationship between heavy alcohol use and pelvic control, DFS, and OS was analyzed using multivariable Cox proportional hazards (PH) regression models. A p-value < 0.05 was considered statistically significant. All analyses were performed with SAS v9.2 (SAS Institute Inc., Cary, NC, USA). Pelvic control was defined as time from diagnosis to last follow up when the patient was free from any recurrence of the cancer. DFS was defined as time from diagnosis to last follow up when the patient had local or distant metastasis. OS was defined as time from diagnosis to either death or last follow up.

Results

Patient Characteristics

The study population consisted of 95 patients with an average age of 54.8 years (range, 27–91 years). 54% of patients were non-smokers, 21% smoked less than 20 pack years, and 25% smoked greater than 20 pack years. The mean age of the study population is 54.8 years with a range of 27 to 91, with 88% of the patients greater than 40. Eighty nine patients (89.5%) were scored as not being heavy drinkers, with 10 patients (10.5%) as heavy drinkers. The patient and tumor characteristics are summarized in Table 1.

Treatment Characteristics

Eighty two percent of patients were treated within 56 days for their external beam and brachytherapy. The majority of patients were treated brachytherapy treatment for an average of 27.3 days. For chemotherapy, 86 patients (90.5%) received cisplatin, 2 patients (2.1%) received 5-fluorouracil (5-FU), and 7 patients (7.4%) did not receive chemotherapy. Of those receiving cisplatin chemotherapy, 79 patients underwent 6 cycles (90.8%), 7 patients underwent 5 cycles (8.0%), and 1 patient underwent 1 cycle (1.2%). Of the two patients receiving 5-FU chemotherapy, both received 2 cycles. All patients underwent EBRT with an average dose of 47.7 Gy (range, 32.4–50.8 Gy). Of those undergoing EBRT, 32 patients received an additional boost dose to areas such as the parametrium and pelvic and/or paraaortic lymph nodes. Fourteen patients (14.7%) were treated with adjuvant hysterectomy after completion of chemoradiation therapy. None of the heavy alcohol patients had an adjuvant hysterectomy, as shown in Table 1.

Outcomes

With a median follow up time of 21 months, , 76% of patients are disease free in the pelvis. 16% of patients experienced local or distant recurrence. 12% of patients died due to cervical cancer, and 15% of patients had a non cervical cancer related death. Univariable Cox PH regression was used to study the relationship/association between pelvic recurrence and each predictor of interest, and indicated that heavy alcohol (>1 drinks per day on average) [P = 0.029; HR 3.10 with 95% CI = (1.13, 8.56)] had a statistically significant effect on pelvic recurrence as shown in Table 3. In addition, heavy alcohol had a statistically significant effect on DFS [P = 0.005; HR 6.19, 95% CI = (1.73, 22.18)]. On multivariable analysis considering the following predictors: smoking, age, ethnicity, Charlson Comorbidity Index, KPS, illicit drug usage, excessive alcohol, lymph node status, FIGO staging, histology,

chemotherapy regimen, radiation treatment time and dose, regression analysis indicated that excessive alcohol (>1 drinks per day on average) [P = 0.005; HR 10.57 with 95% CI = (2.07, 53.93)] had a statistically significant effect on disease free survival as shown in figure 1. Furthermore, univariable Cox PH regression analyses indicated that heavy alcohol (>1 drinks per day on average) [P = 0.001; HR 6.68, 95% CI = (2.10, 21.26)] had a statistically significant effect, respectively, on overall survival as seen in Table 2. Multivariable Cox PH regression was used to study the relationship between OS and predictors based on the stepwise method to select these predictors with the significance level of 0.15 for entry into and staying in the model of 0.15. The multivariable Cox PH regression analysis indicated that excessive alcohol (>1 drinks per day on average) [P = 0.001; HR 10.80, 95% CI = (2.57, 45.40) was statistically significant detriment to OS, as shown in figure 2. In addition, since smoking has been shown to influence cervical cancer outcomes, we explored the effect of smoking on our study population. Comparing smoking without heavy alcohol use patients (37 patients) and the group of smoking with heavy alcohol use patients (7 patients), for comparison of DFS between the two groups, HR (smoking with heavy alcohol use vs. smoking without heavy alcohol use) = 1.37; 95% CI: 0.38–4.99, p = 0.6357; for comparison of DS between the two groups, HR (smoking with heavy alcohol use vs. smoking without heavy alcohol use) = 3.41; 95% CI: 0.91–12.79, p = 0.0688. When examining the two groups as heavy alcohol smokers (7 patients) and the group of heavy alcohol non-smokers (3 patients), for comparison of DFS between the two groups, HR (heavy alcohol smoker vs. heavy alcohol non smoker) = 0; 95% CI: 0-., p = 0.9988; for comparison of DFS between the two groups, HR (heavy alcohol smoker vs. heavy alcohol non smoker) = 0.913; 95% CI: 0.09–8.89, p = 0.9375.

Discussion

The International Agency for Research on Cancer of the World Health Organization has classified alcohol as a Group 1 carcinogen, with high rates of alcohol consumption increasing the risk of developing cancer in multiple organs, including upper gastrointestinal tract, lung, liver, large bowel, and breast[9, 10]. For most of the modern century, medicine has stressed the potential addictive and detrimental health effects of alcohol [9]. However, alcohol, unlike other habit forming addictions such as smoking, has an interesting effect in the body. At low doses, it can exhibit a potentially helpful effect on the body, while at higher doses, lead to cancer and addiction[9]. Alcohol consumption on all cause mortality is illustrated by a J-shaped mortality curve, with the ascending portion of the curve reflecting an increased risk of alcohol-related diseases such as cirrhosis, cardiomyopathy, cancers, and pancreatitis[9, 11, 12]. The association between alcohol consumption and gynecologic malignancy is not well established[11].

Although retrospective in nature with a small number of patients classified as heavy drinkers, our study is hypothesis generating. We show that alcohol consumption was significantly associated with a decreased disease free survival, overall survival, and an increased risk for pelvic recurrence in locally advanced cervical cancer. We also examined the factors of potential treatment delays, with equal percentages within the 2 groups examined with 80% of patients completing within 56 days. The mechanism for alcohol consumption and cervical cancer recurrence is still under investigation. There is, however,

sparse literature on the association of alcohol consumption and the risk of developing cervical cancer[12]. Alcoholism was associated with an increased risk of the development of cervical intraepthielial neoplasia 1 in a study from Korea, p = 0.0001 [13]. In this study, the authors showed that alcohol consumption and high HPV DNA viral load were associated with the risk of CIN1, but not CIN 2/3 or cervical cancer in HPV-positive women[13]. There is likely a multiplicative interaction between HPV viral load and alcohol consumption in cervical carcinogenesis[11, 13]. In addition, previous studies have reported the association between alcohol intake and high grade CIN or cervical cancer [13–15]. Overall, the studies report the aforementioned J shaped association between alcohol consumption and cancer deaths [9, 15]. Therefore, there remains controversy on whether alcohol level is associated with the development of, or a cofactor to cervical carcinogenesis. Our study shows that heavy alcohol consumption increased the risk of DFS and OS. By targeting alcoholism and lifestyle factors, we are placing a focus on survivorship and longevity. Changing a cervical cancer patient's alcohol consumption can lead to improved health.

Although the data investigating the risk of heavy alcohol consumption and association with cervical cancer is not well established, we know that chronic alcohol use is a strong risk factor for a variety of cancers, including those of the head and neck, liver, colorectum, and breast[9, 11]. Potential factors including the primary metabolite of ethanol, acetaldehyde, and oxidative stress could lead to the development of carcinogenesis [16]. DNA methylation is a key factor in epigenetic transcriptional mutations, and a downstream effect could lead to alcohol primed cancer. Futhermore, alcohol can interfere with local DNA methylation mediated by S-adenosylmethionine and its related pathways[16]. There are additional theories on the effect of ethanol to the genome involving one carbon metabolism to increase the risk of carcinogenesis [16].

Gynecologic cancer treatment impacts patient report quality of life and lifestyle behaviors [21]. The purpose of survivorship clinics is for cancer surveillance and general health monitoring to alter long term cancer related outcomes and health related survival[21]. These follow up periods allow for a unique opportunity to investigate current lifestyle behaviors that impact health outcomes. Studies have shown that overall, cancer survivors are less likely than noncancerous controls to be current drinkers, but are more likely to be former drinkers [22]. Given the time constraints of health care providers, ideally one would better identify those patients at highest risk for alcohol dependency. Younger patients in the survivorship period are less likely than older ones to be light, moderate, or heavy alcohol consumers as defined by 1–2, 3–4, >4 drinks per day, 71% vs. 47%, p =0.001, in a recent study by Bifulco et al[21]. Therefore, there may be age differences in the patient population that can allow for a more in depth screening for alcohol dependency or addiction. Midlife adults are less likely to change their alcohol habit after a cancer diagnosis[21]. Confounding the ability to study alcohol consumption in this patient population is the varying degrees of heavy alcohol consumption. In our study, we have chosen the CDC definition of heavy alcohol usage.

At the time of cancer detection, treatment, or follow up visits, our study shows that clinicians need to make a better assessment of patient alcohol use to impact their cancer and overall health. How should we best determine the risk of alcohol dependency in our cervical cancer patients? Studies have shown that clinicians make a poor assessment of alcohol use

as opposed to using validated alcohol risk questionnaires [23]. Four clinical interview questions, the CAGE questions, have proved useful in helping to make a diagnosis of alcoholism[24]. The questions focus on Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers. The acronym “CAGE” helps the physician to recall the questions[24]. The simple mnemonic CAGE makes the 4 questions easy for a busy clinician to remember[24]. The CAGE questionnaire was designed to be a screening tool and not a diagnostic measurement of the amount of drinking, frequency or pattern[25]. There have been more contemporary risk assessment models such as the Michigan Alcohol Screening Test, which consists of 24 questions that inquire about drinking behavior or adverse consequences of alcohol drinking, and the Alcohol Use Disorders Identification Test (AUDIT), which was designed to be sensitive to signs of hazardous and harmful drinking as well as alcohol dependence[26]. Targeted research has shown the brief 5 question AUDIT (AUDIT-5) to perform as well as the more time consuming AUDIT for patients with alcohol dependency or addiction [27]. To follow up the CAGE questionnaire, soliciting patients how the amount and frequency of alcohol use usually leads to an estimate lower than the actual number of alcoholic drinks per day. Thus, patients who admit to only 2 or 3 drinks per day may be giving an underestimate to themselves and clinicians. Therefore, an option for a busy clinician is to screen patients with the CAGE questionnaire, and then follow up with an AUDIT-5 questionnaire, as shown in Figure 3.

The degree to which physicians tend to overlook alcoholism and other addictions is substantial with a major effect on cancer recurrence, and major health consequences in the survivorship phase of treatment [22, 28]. A recent study showed that alcoholism is highly prevalent and frequently under diagnosed in patients with advanced cancer [28]. Alcohol dependency and addiction responds to treatment when discovered. In addition, in our patient population, more of the heavy alcohol patients were also concurrent smokers. Patients can be treated with psychotherapy, medication, and self-help programs such as Alcoholics Anonymous, which can increase quality of life and promote health. Clinical trials have continued to demonstrate the benefits of alcohol treatment in promoting abstinence or reduced heavy drinking for an increased quality of life[25].

Our current study suffers from the limitations associated with a retrospective review with the accompanying problems of selection bias and potential for incomplete data records. In addition, our data is from a single institution with small number of patients classified as being heavy drinkers. However, to minimize selection bias confounding we included consecutively treated patients. In addition, our follow up period was 36 months, which captures most of cervical cancer failures as the disease recurrence rates are highest in the first 2 years after treatment. Furthermore, our alcohol categorization is based on our social history collection clinical form and did not include the alcohol screening or dependency validated questionnaires such as the CAGE, AUDIT, or AUDIT-5.

Conclusion

In this small series of patients with heavy alcohol use, the data suggests supports the association that heavy alcohol use increases the risk of cervical cancer recurrence and

mortality. Addition research and physician attention should be made to elicit accurate alcohol usage to target alcoholism in this patient population to promote increased survival.

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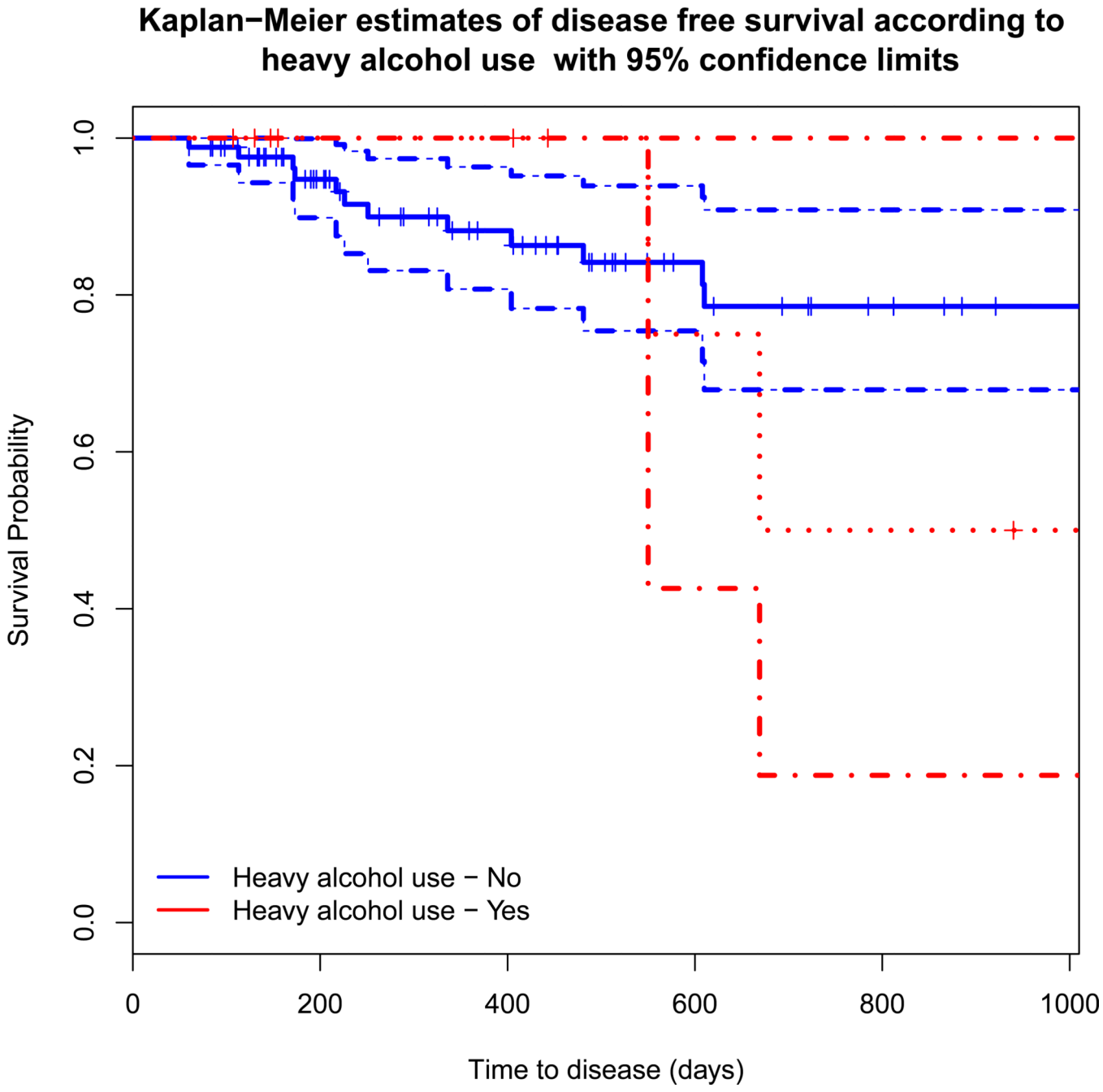

Figure 1.
Kaplan Meir disease free survival curve

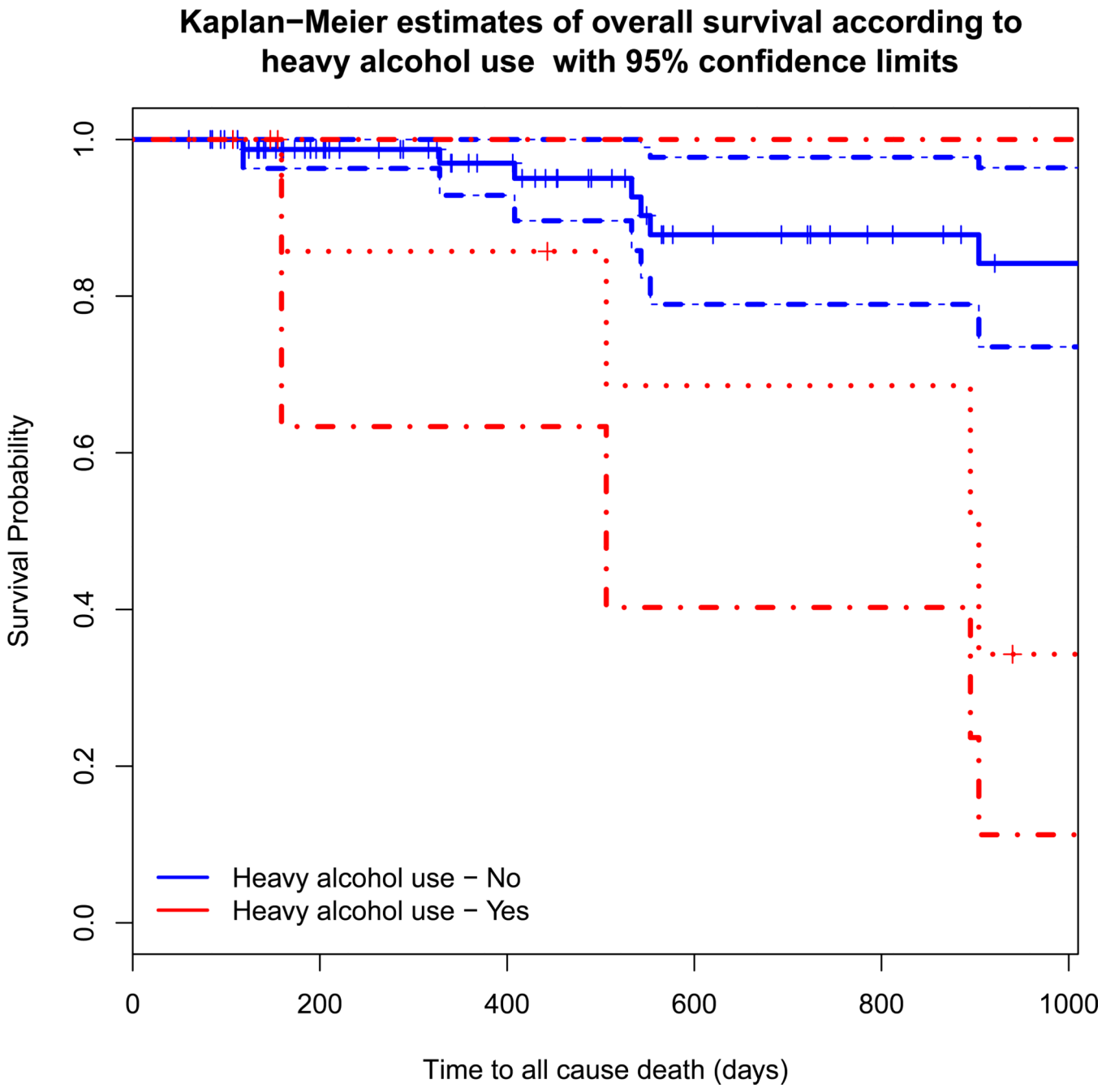

Figure 2.
Kaplan Meir overall survival curve

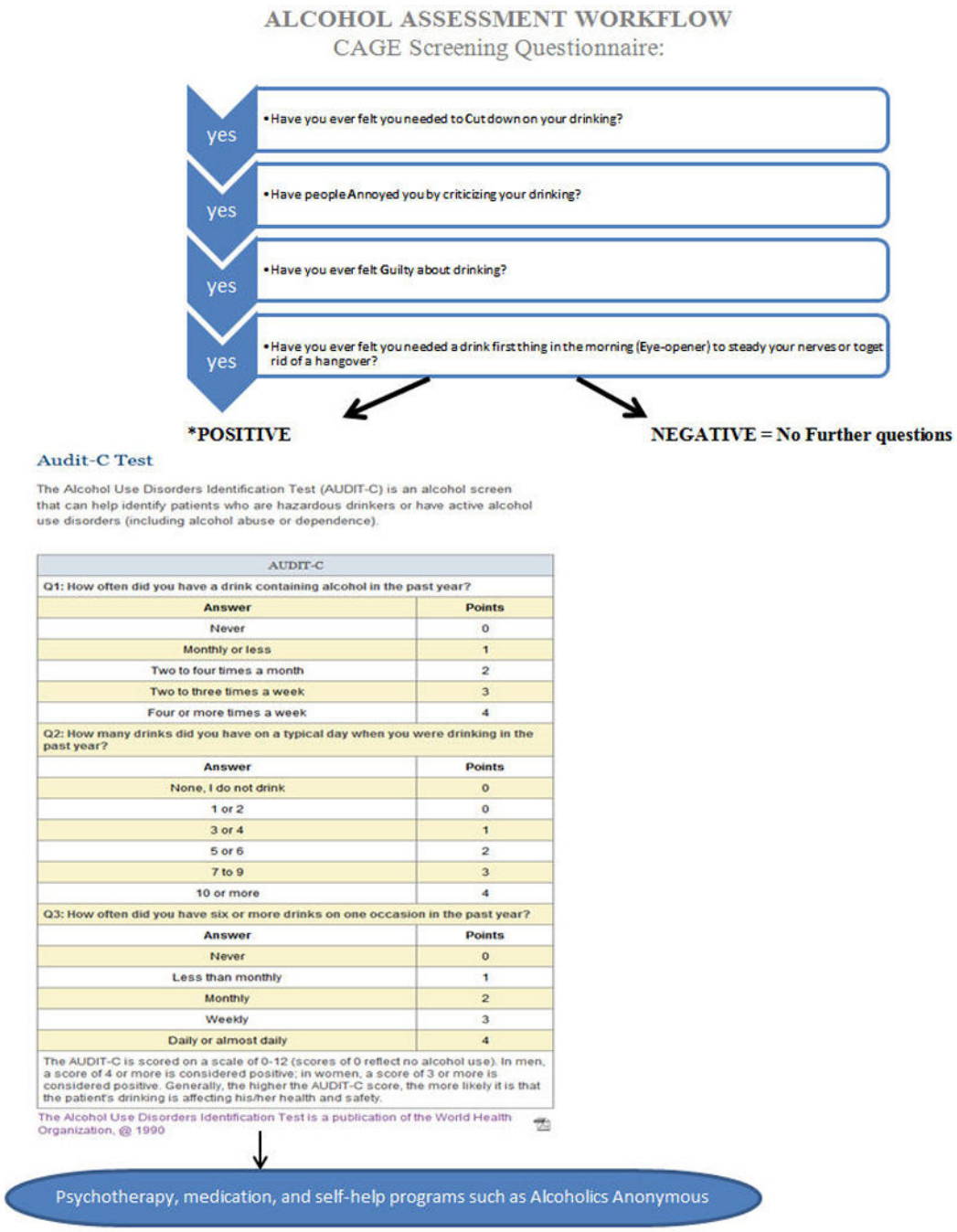

Figure 3.
Workflow alcohol assessment

Table 1

Patient and Disease Characteristics

Patient/Disease Characteristics	Not heavy alcohol use	Heavy Alcohol Use
Patients	Number (% population)	Number (% population)
Total Number	85	10
Smoking in Pack Years		
Mean (SD)	11.0 (16.1)	19 (23.5)
Age (Years)		
Mean (SD)	54.5 (12.8)	58.0 (13.1)
Frequency of Grouped Charleson Comorbidity Index (%)		
Charleson comorbidity Index		
2	63 (75.3%)	10 (100%)
3 or 4	21 (24.7%)	0 (0%)
Frequency of Grouped KPS Score (%)		
≤ 80	14 (16.5%)	4 (40.0%)
>80 and <100	66 (77.7%)	6 (60.0%)
100	5 (5.9%)	0 (0.0%)
Frequency of Grouped LN Status (%)		
None	59 (69.4%)	8 (80.0%)
Positive	26 (30.6%)	2 (20.0%)
Frequency of Grouped Stage (%)		
IB1, IB2, IIA	27 (31.8%)	2 (20.0%)
IIB, IIIA	45 (52.9%)	4 (40.0%)
IIIB	13 (15.3%)	4 (40.0%)
Frequency of Grouped Histology (%)		
Squamous cell carcinoma	70 (82.4%)	8 (80.0%)
Adenocarcinoma, adenosquamous, or poorly differentiated neuroendocrine	15 (17.7%)	2 (20.0%)
Total radiation treatment time		
Greater than 56 days	15 (17.7%)	2 (20.0%)
Less than 56 days	70 (82.4%)	8 (80.0%)
Frequency of Grouped Chemotherapy Regimen (%)		
None	6 (7.1%)	1 (10.0%)
Cisplatin or 5-Flurouracil	79 (92.9%)	9 (90.0%)
Frequency of Grouped Number of Chemo Cycles (%)		
0	6 (7.1%)	1 (10.0%)
4 or 5	7 (8.2%)	1 (10.0%)
6	72 (84.7%)	8 (80.0%)
Frequency of Grouped External Beam Radiation Therapy Dose (%)		
EBRT Dose		
<5000	66 (77.7%)	8 (80.0%)

Patient/Disease Characteristics	Not heavy alcohol use	Heavy Alcohol Use
≥5000	19 (22.4%)	2 (20.0%)
Frequency of Parametria Boost (%)		
No boost	44 (51.8%)	4 (40.0%)
Boost delivered	41 (48.2%)	6 (60.0%)

Table 2

Univariable and Multivariable Analysis for Excessive Alcohol come

	Univariable Analysis			Multivariable Analysis		
	HR	**95% CI for HR**	**P-value**	**HR**	**95% CI for HR**	**P-value**
Pelvic Failure	3.10	(1.13,8.56)	0.029			
Disease Free Survival	6.19	(1.73,22.18)	0.005	10.57	(2.07,53.93)	0.005
Overall Survival	6.68	(2.10,21.26)	0.001	10.80	(2.57,45.40)	0.001