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Intensive care unit stay is prolonged in chronic alcoholic men following tumor resection of the upper digestive tract

C. D. SPIES[1], A. NORDMANN[1], G. BRUMMER[1], C. MARKS[2], C. CONRAD[3], G. BERGER[4], N. RUNKEL[4], T. NEUMANN[1], C. MÜLLER[5], H. ROMMELSPACHER[6], M. SPECHT[1], L. HANNEMANN[1], H. W. STRIEBEL[1] and W. SCHAFFARTZIK[1]

Departments of [1]Anesthesiology and Operative Intensive Care Medicine, [2]Facial and Maxillofacial Surgery, [3]ENT, [4]Abdominal, Vascular and Thoracic Surgery, Benjamin Franklin Medical Center, Departments of [5]Clinical Chemistry and Biochemistry and [6]Neuropsychopharmacology, Rudolf Virchow Medical Center, Free University, Berlin

Background: The prevalence of chronic alcohol misuse in patients with oral, pharyngeal, laryngeal or esophageal carcinomas exceeds 60%. No data is available, to our knowledge, on the morbidity and mortality of chronic alcoholics in surgical intensive care units (ICU) following tumor resection. We investigated whether the subsequent ICU stay in chronic alcoholics following tumor resection was prolonged and whether the incidence of pneumonia and sepsis was increased.

Methods: 213 patients with carcinomas of the upper digestive tract were evaluated regarding their drinking habits. Chronic alcoholics met either the DSM-III-R criteria for alcohol abuse or dependence. Conventional laboratory markers and serum carbohydrate-deficient transferrin were determined preoperatively. Major intercurrent complications during ICU stay such as an alcohol withdrawal syndrome, pneumonia and sepsis as well as the frequency of death were documented.

Results: Patients did not differ significantly between groups regarding age or APACHE score on admission to the ICU. 121 patients were diagnosed as being chronic alcoholics, 39 as being social drinkers and 61 as being non-alcoholics. In chronic alcoholics the frequency of death was significantly increased. Due to the increased incidence of pneumonia and sepsis the ICU stay was significantly prolonged in chronic alcoholics by approximately 8 days.

Conclusions: The increased mortality and morbidity rate demonstrates that chronic alcoholics undergoing major tumor surgery have to be considered as high-risk patients during their postoperative ICU stay. Further studies are required with respect to the immuno-competence of chronic alcoholics and the prevention of alcohol withdrawal syndrome, pneumonia and sepsis in these patients.

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An increased risk of oral, pharyngeal and extrinsic laryngeal carcinomas is reported with chronic alcohol consumption [1-4]. Seitz & Simanowski [2] demonstrated that 92% of patients with oral carcinomas were chronic alcoholics. The prevalence of alcohol misuse in patients with esophageal carcinoma was reported to be 61% [2]. Chronic alcoholics run an increased risk, especially in the postoperative period, of developing alcoholism-related complications. Tonnesen et al. [5] reported that the postoperative morbidity was increased and the hospital stay was significantly prolonged in chronic alcohol abusers after elective resection of the colon or rectum. These patients were not admitted to the intensive care unit postoperatively. Jensen et al. [6] found in ICU patients that the mortality rate of chronic alcoholics was 50% compared with 26% of patients who did not misuse alcohol before they were admitted to the ICU. However, the patient population in the study performed by Jensen et al. [6] was heterogeneous and not even half of these patients underwent operations.

We investigated whether the ICU stay was prolonged in chronic alcoholics following tumor resection of the upper digestive tract, and whether the incidence of pneumonia and sepsis as well as the frequency of death was increased during ICU stay. The rationale for this study was that on one hand chronic alcoholics are reported to have an altered immune system [7,8], which may play a role in the development of these complications during the ICU stay. On the other hand, altered cytokine levels have also been implicated in the development of pneumonia and the degree of pulmonary dysfunction [9]. A sev-

eral-fold increased complication rate is found in ICU patients frequently related to abnormal immunity, invasive monitoring and multiple procedures [6, 9-12].

Methods

Patients

In this prospective clinical trial 213 consecutive male patients with carcinomas of the upper digestive tract admitted to the ICU following tumor resection were included. Women and patients under the age of 18 were excluded from the study. The patients gave their written informed consent to participate in this study approved by our ethics committee. Patients' basic characteristics such as age, height, weight, Acute Physiology and Chronic Health Evaluation scoring (APACHE III) [13] and Multiple Organ Failure Score (MOF) [14] were documented (Table 1-3).

Diagnosis of chronic alcohol abuse and alcohol dependence

The patient's history and an alcoholism-related questionnaire, the CAGE Questionnaire (see appendix) [15], were obtained from the patients preoperatively. All chronic alcoholics met either the DSM-III-R criteria (see appendix) [16] for alcohol abuse or dependence or developed an alcohol withdrawal syndrome (AWS) during their ICU stay [16,17]. Alcohol-dependent patients, if diagnosed preoperatively, were treated with a pharmaco-prophylaxis to prevent an AWS in the ICU. If AWS developed they were managed accordingly. Patients with a daily ethanol intake ≤25g and a CAGE = 0 were considered to be non-alcoholics without risk of developing postoperative alcoholism-related complications. Patients with a daily ethanol intake between 25 and 60 g and who had a CAGE of 1 or 2 were considered social drinkers. The investigator responsible for the alcoholism-related history was blinded to the documentation of the intercurrent complications during the ICU stay.

Laboratory markers

Preoperatively, blood samples for the conventional laboratory markers and for carbohydrate-deficient transferrin (CDT) were drawn. CDT are isoforms deficient of carbohydrate moieties. After more than a week a chronic daily intake of more than 60 g alcohol leads to increased levels of transferrin isoforms. With abstinence from alcohol the values normalize with a mean half life of 14 to 17 days [18]. However, in chronic alcoholics undergoing operations the half life is reported to be shorter [19]. The blood required to determine CDT was immediately centrifuged at 3000 RPM for 10 min. The serum was then separated and cooled to –80°C. The serum CDT was determined by microanion exchange chromatography (MAEC) and subsequent turbidimetry [20]. A CDT above 9 mg/l was defined as pathologically elevated [21]. Conventional laboratory parameters such as γ-glutamyl-transferase (GGT) and mean corpuscular volume (MCV) (Table 1) were determined according to clinical routine.

Investigational protocol

Diagnoses, intensive care treatment (i.e. medications), operations and the length of ICU stay were documented. Fluid administration (cristalloids, colloids, blood transfusions) was recorded perioperatively and during the subsequent ICU stay. Vital signs, laboratory markers and postoperative complications were documented. Infections were determined according to the criteria recommended by the Centers for Disease Control and Prevention (CDC) [22]. Pneumonia was diagnosed by new onset of purulent sputum or change in character of sputum and rales or dullness to percussion on examination present in an area corresponding with an infiltrate evident on a chest radiograph. Organisms isolated from specimens obtained by endotracheal suctioning or bronchial alveolar lavage are given in Table 2. Sepsis was defined according to the Society of Critical Care Medicine Consensus Conference [23]. Perioperative antibiotic prophylaxis with cefotiam was routinely administered to all patients. Further antibiotic therapy was administered according to the susceptibility of the organism isolated during the ICU stay. If the patient developed a pneumonia and no organism was isolated, cefotaxim and gentamicin were administered. Once the infectious process was under control, it was vigorously attempted to wean patients from ventilatory support.

The differential diagnosis of AWS was performed according to an accepted algorithm [24]. A shortened 10-item scale, the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar), for clinical quantitation of the severity of alcohol withdrawal syndrome was used [25]. The CIWA-Ar is a 10-item/67-point scale for measurement of the degree of AWS, including vegetative symptoms, hallucinations and symptoms of delirium tremens. Pharmacological treatment is not indicated for a score <10. Clinical judgement will determine whether

drugs should be given for scores of 10 to 20. Pharmacological treatment is indicated for scores ≥20 [25]. Diagnosis was confirmed by a participating neurology consultant. Symptoms were documented in the study protocol. If the diagnosis of AWS was established, a bolus of flunitrazepam was administered to control agitation. Then to control persistent vegetative symptoms, clonidine (up to a total dose of 1.2 mg), and to control hallucinations, haloperidol (up to a total dose of 40 mg), were administered. If, following this therapy, symptoms were not adequately blocked, another flunitrazepam bolus was given until the CIWA-Ar was < 20. Maintenance therapy was adapted to achieve a CIWA-Ar < 10. The maintenance therapy was guided with respect to the occurrence of symptoms. If vegetative symptoms were present the infusion rate of clonidine was increased, if hallucinations were present the infusion rate of haloperidol was increased (up to a total dose of 240 mg per day) and if delirious symptoms and agitation were present the infusion rate of flunitrazepam was increased. If alcohol dependence was diagnosed preoperatively, prophylaxis was administered immediately postoperatively by a bolus of flunitrazepam followed by a continuous infusion. The regimen was adapted so that the patients were always arousable while a CIWA-Ar < 20 was maintained. If AWS developed, therapy was initiated as stated above.

Statistical analysis

All data was expressed as mean±SD if normally distributed (Kolmogoroff-Smirnoff test), otherwise as median and range. Sensitivity was calculated as the ratio of the number of chronic alcoholics with a positive test divided by the number of all chronic alcoholics. Specificity was calculated as the ratio of non-alcoholics with a negative test divided by the number of all non-alcoholics. Statistical analysis was performed by ANOVA, if normally distributed, or the Kruskal-Wallis test. To compare dichotomous variables the k2-X^2-test of Brandt and Snedecor was used. If statistical significance was obtained by any of these multivariate tests, the independent samples *t*-test (ANOVA), the Wilcoxon signed rank sum test (Kruskal-Wallis test) or the X^2-test (k2-X^2-test) were used to further determine intergroup differences. The study was designed with a power of 0.8 to detect differences between groups in the incidence of pneumonia and sepsis and the frequency of death. A $P \leq 0.05$ was considered significant.

Results

Chronic alcoholics (n=121), social drinkers (n=39) and non-alcoholics (n=61) differed in alcoholism- related history, serum GGT and CDT (Table 1). Sensitivity of CDT was 58% and specificity 90%; sensitivity of GGT was 59% and specificity 72%. The groups did not differ significantly with respect to their preoperative additional diagnoses such as chronic obstructive lung disease (chronic alcoholics: 54/121, social drinkers: 10/39, non-alcoholics: 9/61), congestive heart failure (chronic alcoholics: 9/121, social drinkers: 1/39, non-alcoholics: 1/61), arterial hypertension (chronic alcoholics: 25/121, social drinkers: 5/39, non-alcoholics: 9/61), ischemic heart disease (chronic alcoholics: 16/121, social drinkers: 3/39, non-alcoholics: 7/61), myocardial infarction (chronic

Table 1

Basic patient characteristics and alcoholism-related history

	units	Chronic alcoholics I (n=121)	Social drinkers II (n=39)	Non-alcoholics III (n=61)	*P*
age	years	56±9	54±9	55±11	0.3134
height	cm	174±5	175±5	174±8	0.6541
weight	kg	72±16	73±11	76±14	0.1410
ethanol intake	g day^{-1}	133±93	43±8	4±5	0.0000 I-II, I-III, II-III
CAGE		3±1	1±1	0±0	0.0000 I-II, I-III, II-III
CDT	mg l^{-1}	12 (2–68)	7 (2–34)	4 (2–26)	0.0107 I-II, I-III
GGT	katal l^{-1}	44 (10–393)	19 (8–100)	24 (5–97)	0.0004 I-II, I-III
MCV	fl	96.4±0.9	95.6±1.3	93.5±0.7	0.0800

mean±SD; median (range) frequency (%); *P*: multivariate *P*, I-II, II-III or I-III; bivariate significance; CAGE: alcoholism-related questionnaire; CDT: carbohydrate-deficient transferrin (cut-off 9 mg l^{-1}); GGT: γ-glutamyl transferase; MCV: mean corpuscular volume.

Table 2

ICU and major intercurrent complications

	units	Chronic alcoholics I (n=121)	Social drinkers II (n=39)	Non-alcoholics III (n=61)	*P*
APACHE III on admission ICU		40±11	39±8	36±10	0.3742
MOF on admission ICU		2.3±2.0	2.1±1.4	1.9±1.3	0.2322
mechanical ventilation on admission	n (%)	118 (98%)	38 (97%)	59 (97%)	0.9880
highest APACHE III (during ICU stay)		56±43	39±9	40±11	0.0134 I-II, I-III
highest MOF (during ICU stay)		4±3	3±1	3±1	0.0000 I-II, I-III
period of mechanical ventilation	days	6±13	1±1	1±1	0.0010 I-II, I-III
pneumonia	n (%)	46 (38%)	4 (10%)	4 (7%)	0.0000 I-II, I-III
mechanical ventilation	n (%)	31 (67%)	2 (50%)	2 (50%)	
worst $Pa0_2/FIO_2$	kPa	34±9	39±10	37±11	
temperature (max)	°C	38.9±0.6	39.1±0.5	39.0±0.4	
WBC (max)	$g\ l^{-1}$	16.3±5.8	18.2±2.8	19.1±2.5	
organisms isolated	n				
Pseudomonas aeruginosa		5	1	1	
Staphylococcus aureus		2	0	0	
Haemophilus influenzae		1	0	0	
Klebsiella pneumoniae		2	0	1	
other gram-negative		1	0	1	
other gram-positive		1	0	0	
Candida		1	0	0	
sepsis	n (%)	16 (13%)	0 (0%)	0 (0%)	0.0014 I-II, I-III
oxygen consumption	$ml\ min^{-1}\ m^{-2}$	109 (43–168)			
oxygen delivery	$ml\ min^{-1}\ m^{-2}$	775 (468–1053)			
lactate (max)	$mmol\ l^{-1}$	2.4 (1.3–6.9)			
death	n (%)	9 (7%)	0 (0%)	0 (0%)	0.0438 I-II, I-III

mean±SD; median (range); frequency (%); *P*; multivariate *P*, I-II, II-III or I-III; bivariate significance; max=maximum; min-minimum; APACHE: Acute Physiology and Chronic Health Evaluation score; MOF=Multiple Organ Failure Score; PAO_2/FIO_2-arterial oxygen tension/inspired oxygen fraction ratio.

alcoholics: 12/121, social drinkers: 3/39, non-alcoholics: 5/61), gastritis (chronic alcoholics: 39/121, social drinkers: 7/39, non-alcoholics: 13/61), liver disease (chronic alcoholics: 8/121, social drinkers: 2/39, non-alcoholics: 2/61) and diabetes mellitus (chronic alcoholics: 13/121, social drinkers: 4/39, non-alcoholics: 7/61). The type of surgery and the APACHE III or MOF scores on admission to the ICU did not significantly differ between groups (Table 2).

During their ICU stay chronic alcoholics developed more frequently pneumonia and sepsis, requiring a prolonged ICU stay (Fig. 1, Table 2). The mortality rate was significantly increased in chronic alcoholics (Table 2). Major surgical complications (anastomotic leakage or necrosis of transplant) only occurred in chronic alcoholics (10/121=8%; P=0.0286). The number of operations required secondary to surgical complications or bleeding disorders was significantly increased in chronic alcoholics (chronic alcoholics: 28/121 (23%); social drinkers 3/39 (8%); non-alcoholics 4/61 (7%); P=0.0151).

Of the chronic alcoholics 70 (70/121=58%) were alcohol dependent; 48 of these (48/70=69%) were diagnosed preoperatively and received pharmaco-prophylxis to prevent AWS (Table 3). Twenty-two (22/70=31%) were not diagnosed as alcohol dependent and developed an AWS during their subsequent ICU stay (Table 3). Fifty-one chronic alcoholics (51/121=42%) were chronic abusers as diagnosed by DSM-III-R. These patients did not receive any pharmaco-prophylaxis and did not develop an AWS during their ICU stay (Table 3). Only the CAGE questionnaire and not the conventional laboratory markers differed between chronic alcoholics who were alcohol dependent and received pharmaco-prophylaxis to prevent AWS and those who were chronic alcohol abusers (Table 3). However, the CAGE did not differ between alcohol-dependent patients who sub-

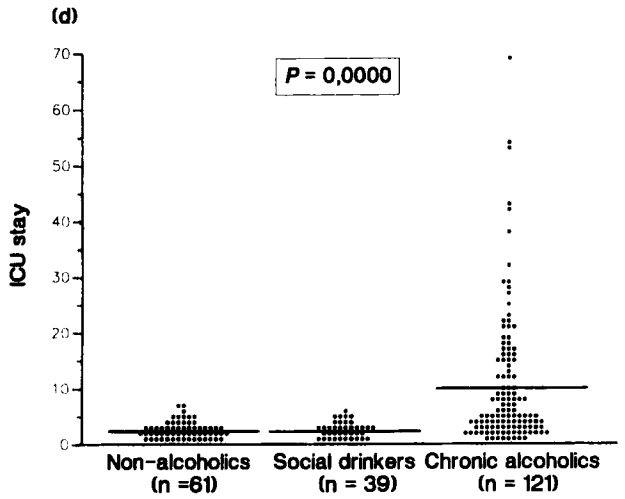

Fig. 1. Intensive care unit (ICU) stay in chronic alcoholics, social drinkers and non-alcoholics.

sequently developed AWS during ICU stay and those who were chronic alcohol abusers (Table 3). Alcohol-dependent patients who were not preoperatively diagnosed as alcohol dependent and who developed AWS underwent a significantly prolonged ICU stay and had the highest incidence of postoperative alcoholism-related complications (Table 3).

If alcohol-dependent patients developed AWS, the initial flunitrazepam bolus required to block the symptoms of AWS adequately to achieve a CIWA-Ar < 20 was significantly lower in the prophylactically (0.8 mg (range: 0.4–3.5 mg)) than in the therapeutically treated group (4.5 mg (0.5–20.0 mg); P=0.0001). Also, the maximal infusion rate for maintenance therapy was significantly decreased in the prophylactically treated group (prophylactically treated group: 8.1 $\mu g \cdot kg^{-1}$ min^{-1} (1.2–73.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), therapeutically treated group: 24.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (2.8–301.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$; P=0.0001). Requirements for additional medication such as haloperidol (prophylactically treated group: 2/12, therapeutically treated group: 13/22; P=0.0025) and clonidine (prophylactically treated group: 5/12, therapeutically treated group: 20/22; P=0.0107) differed significantly between both groups if AWS developed.

Discussion

Chronic alcoholics developed more major intercurrent complications and required prolonged ICU treatment. The ICU stay was prolonged by approximately 8 days in chronic alcoholics. On admission to the ICU mechanical ventilatory support was initially required in most of the patients following tumor resections. Intubation has been reported to result in a 7- to 10-fold increase in the incidence of nosocomial

Table 3

Patients with chronic alcohol misuse (n=121)

		Dependence		Chronic abuse	
		prophylaxis I	therapy II	III	
	units	(n=48)	(n=22)	(n=51)	*P*
CAGE		3.4±0.1	2.6±0.5	2.4±0.9	0.0000 I-II, I-III
CDT (on admission)	mg l^{-1}	12 (2–68)	11 (2–43)	17 (4–33)	0.2924
GGT (on admission)	katal l^{-1}	44 (13–393)	62 (13–255)	39 (10–339)	0.2750
ICU stay	days	5±7	19±16	6±5	0.0000 I-II, II-III
period of mechanical ventilation	days	1±1	16±14	2±2	0.0001 I-II, II-III
withdrawal	n (%)	12 (25%)	22 (100%)	0 (0%)	0.0000 I-II, I-III, II-III
period between admission and beginning of AWS	days	4.2±2.2	2.4±4.4		0.0000 I-II
CIWA-Ar		32±8 (n=12)	48±11		0.0000 I-II
pneumonia	n (%)	7 (15%)	18 (82%)	21 (41%)	0.0000 I-II, I-III, II-III
sepsis	n (%)	3 (6%)	7 (32%)	6 (12%)	0.0442 I-II, II-III
death	n (%)	2 (4%)	4 (18%)	3 (6%)	0.1945

mean±SD; median (range); frequency (%); *P*: multivariate *P*, I-II, II-III or I-III: bivariate significance; CAGE: alcoholism related questionnaire; CDT: carbohydrate-deficient transferrin (cut-off 9 mg l^{-1}); GGT: γ-glutamyl transferase; ICU=intensive care unit; CIWA-Ar: the revised clinical institute withdrawal assessment for alcohol scale.

pneumonia [26,27], which may partly explain the overall increased incidence of pneumonia in the investigated patients compared to peripheral surgical wards [5,10]. Craven et al. [28] have demonstrated that mechanical ventilation in a high-risk patient is in itself a risk factor increasing the mortality of pneumonia.

Only chronic alcoholics developed a sepsis following tumor resection. This may be due to a pre-existing altered immuno-competence of chronic alcoholics [7,8], a deficit in substances involved in the healing process [29], or to a decreased blood flow due to perfusion abnormalities [5,30,31], so that chronic alcoholics are more prone to develop sepsis. It is crucial to realize that bacteremia due to the host response may cause no harm or lead to multiple organ failure and death [11].

The severity of pre-exisiting illness has been demonstrated to be strongly associated with the risk of developing nosocomial infections [9,12]. Except for chronic alcohol misue the patients did not differ significantly between groups regarding their pre-existing diseases. However, this study was designed with a power of 0.8 to detect differences between groups in the ICU stay and major common complications. Therefore, it cannot be ruled out that the power to detect for differences in the preoperative additional diagnosis was not enough. All of our patients had carcinomas, all patients had already undergone an initial insult i.e. intubation and surgery, and were, therefore, at risk of an overwhelming and a potentially worse response to bacteremia [32].

The worst outcome i.e. the longest ICU stay and the highest incidence of pneumonia and sepsis was observed in chronic alcoholics following the onset of an AWS. Chronic alcoholics who were not diagnosed preoperatively as being alcohol dependent and, therefore, received no prophylaxis, required a prolonged ICU stay by approximately 13 to 14 days compared to those alcohol-dependent patients who received pharmaco-prophylaxis or those who were chronic alcohol abusers. The difference between alcohol-dependent patients and chronic alcohol abusers is evident with respect to the fact that the latter do not develop AWS and, therefore, do not need any additional respiratory depressant treatment to counteract the symptoms of alcohol withdrawal. The difference between alcohol-dependent patients who were treated prophylactically vs. those who were treated therapeutically is more complex due to the fact that, on one hand, it cannot be ruled out that these results are biased. As withholding prophylaxis in alcohol-dependent patients would lengthen ICU stay [21] this was deemed unethical. Therefore, if alcohol dependence was diagnosed preoperatively the patient was treated prophylactically. On the other hand, all alcohol-dependent patients who developed AWS and who were not diagnosed as being alcohol dependent preoperatively developed a more severe AWS as evaluated by a standardized variable, the CIWA-Ar, than that found in the prophylactically treated alcohol-dependent patients of whom 25% developed AWS during the ICU stay. This may be due to the fact that the required dosages of benzodiazepines (bolus and maximal infusion rate for maintenance therapy) as well as the need for additional drugs such as haloperidol and clonidine were significantly increased in the therapeutically treated patients to control the symptoms of alcohol withdrawal than in the prophylactically treated patients who developed AWS. Therefore, more patients in the therapeutically treated group developed respiratory depression and required mechanical ventilation for a preliminary period during AWS. These findings may be a hint that preoperative diagnosis of alcohol dependence and postoperative prophylaxis may reduce the incidence or severity of AWS and may shorten ICU stay. However, this requires further investigation.

The problem still remains to diagnose alcohol-dependent patients preoperatively. It is reported that only 16%-23% of the surgical patients who are chronic alcoholics are routinely detected clinically [33,34]. If the patient has been seen several times preoperatively, i.e. three times in the previous study, the rate has been increased to 34% [34]. In the present study, however, a higher rate of 69% of the alcohol-dependent patients were diagnosed preoperatively. This may be due to the fact that on one hand the CAGE questionnaire, designed as one of the screening devices for alcoholism in many treatment and research programs, was used [15, 34-36]. The CAGE questionnaire is short, precise and practicable. Time-consuming alcoholism-related questionnaires [16,36] are not practicable in clinical routine. Buchsbaum et al. [35] found a good correlation between the CAGE questionnaire and the DSM-III-R criteria of alcohol dependence [16]. On the other hand, however, all questionnaires depend on the cooperation of the patient and therefore not all alcohol-dependent patients were identified preoperatively. As has been shown previously [34], the CAGE questionnaire alone increased the rate of detecting alcohol-dependent patients up to 64%; the combination

of the CAGE questionnaire and the laboratory markers GGT and CDT increased the rate up to 91%.

The GGT and a more recent biological marker, CDT, differed significantly between groups and could assist in making a preoperative diagnosis, despite the fact that the sensitivites and specificities reported for CDT and GGT are lower than in the range observed with previous studies [18]. However, increased serum levels of these markers have been used as biological markers of excessive alcohol consumption and did not differ between chronic alcoholics who are alcohol dependent and those who are not [18,19,21]. Therefore, preoperatively elevated serum CDT and GGT values can only be used as indicators for further patient evaluation. Pathologically elevated CDT and GGT values and subsequent evaluation may alter the management of patients in the ICU and prevent postoperative alcohol-related complications.

In conclusion, this study demonstrated that chronic alcoholics underwent a prolonged ICU stay due to an increased postoperative morbidity. It is of major impact, in our view, that only the chronic alcoholics died during their subsequent ICU stay following tumor resection. The one major complication i.e. AWS may be prevented or at least the severity can be reduced by pharmaco-prophylaxis in alcohol-dependent patients if diagnosed preoperatively. However, this requires further investigation. Since no laboratory marker is available which identifies patients who will develop AWS, further studies are required to find diagnostic parameters to detect alcohol-dependent patients. Since pneumonia and sepsis were significantly more frequent in chronic alcoholics, research with respect to alterations in the immune status in chronic alcoholics should be intensified.

Appendix

CAGE QUESTIONNAIRE [15]: It concentrates on the social and physical consequences of alcohol misuse and consists of four questions ("yes" = 1 point, "no" = 0 points, total: 0 - 4 points):

- Have you ever felt you should cut down on your drinking ?
- Have other people annoyed you by criticising your drinking ?
- Have you ever felt guilty about drinking ?
- Have you ever taken a drink in the morning to steady your nerves or get rid of a hangover (eye opener) ?

DSM-III-R [16]: *Criteria for Alcohol Dependence*

A. At least three of the following:

1) Marked tolerance - need for markedly increased amounts of alcohol (i.e. at least 50% increase) in order to achieve intoxication, desired effect, or markedly diminished effect with continued use of the same amount of alcohol.
2) Characteristic withdrawal symptoms for alcohol.
3) Alcohol often taken to relieve or avoid withdrawal symptoms.
4) Persistent desire or one or more unsuccessful efforts to cut down or control drinking.
5) Drinking in larger amounts or over a longer period than the person intended.
6) Important social, occupational, or recreational activities given up or reduced because of drinking.
7) Frequent intoxication or withdrawal symptoms when expected to fulfil major role obligations at work, school, or home or when drinking is physically hazardous.
8) Continued drinking despite knowledge of having a persistent or recurring social, psychological, or physical problem that is caused or exacerbated by alcohol use.
9) A great deal of time spent in activities necessary to obtain alcohol, to drink or to recover from its effects.

B. Some symptoms of the disturbance have persisted for at least one month or have occurred repeatedly over a longer period of time.

DSM-III-R [16]: *Criteria for Chronic Alcohol Abuse*

A. A maladaptive pattern of alcohol use indicated by at least one of the following:

1) Continued drinking despite knowledge of having a persistent or recurring social, psychological, or physical problem that is caused or exacerbated by alcohol use.
2) Recurrent drinking in situations in which it is physically hazardous.

B. Some symptoms of the disturbance have persisted for at least one month or have occurred repeatedly over a longer period of time.

C. Never met the criteria for alcohol dependence.

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Address:
Claudia Spies, MD
Klinik für Anaesthesiologie und Operative Intensivmedizin
Universitätsklinikum Benjamin Franklin
Freie Universität Berlin
Hindenburgdamm 30
12200 Berlin
Germany