Strahlenther Onkol (2016) 192:552–560
DOI 10.1007/s00066-016-0999-3

ORIGINAL ARTICLE

Haemoglobin and creatinine values as prognostic factors for outcome of concurrent radiochemotherapy in locally advanced head and neck cancers

Secondary results of two European randomized phase III trials (ARO 95-06, SAKK 10/94)

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Received: 7 March 2016 / Accepted: 10 May 2016 / Published online: 20 June 2016

Abstract

Background To determine the influence of baseline laboratory values on treatment outcome in patients with locally advanced head and neck cancer (HNSCC).

Methods Data of the randomized trials ARO 95 -06 (n = 384) and SAKK 10 /94 (n = 224) were pooled for a total sample size of 608 patients. Haemoglobin (Hb) and creatinine (Cr) were available at baseline and their association

Electronic supplementary material The online version of this article (doi: 10.1007/s00066-016-0999-3) contains supplementary material, which is available to authorized users.

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with locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS) was analyzed using univariable and multivariable Cox regression models.
Results A total of 580 and 564 patients were available with baseline Hb and Cr values in the pooled analysis. Univariable analyses revealed that lower baseline Hb values were significantly associated with decreased LRRFS, DMFS, CSS and OS. This effect remained significant for OS when the treatment arms (radiotherapy [RT] alone vs. chemoradiation [CRT]) were analyzed separately. Higher baseline Cr was associated with improved OS in the pooled analysis. Interestingly, the prognostic value of baseline Cr appeared to be limited to the subgroup of 284 patients who were treated with CRT. In the multivariable Cox regression model lower baseline Hb remained associated with decreased OS both in the patients who received CRT (HR 0.79, 95 % CI 0.66–0.94, $p = 0.009$) and in those patients who underwent RT alone (HR 0.67, 95 % CI 0.58–0.78, $p < 0.001$). Increased baseline Cr remained significantly associated with improved OS in patients who underwent CRT (HR 0.79, 95 % CI 0.69–0.92, $p = 0.002$) but not in those patients who underwent RT alone.
Conclusions An association between lower baseline Hb and inferior treatment outcome was confirmed. Baseline Cr was introduced as a prognosticator of outcome after CRT for locally advanced HNSCC.

Keywords Carcinoma, squamous cell of head and neck · Radiation therapy · Chemotherapy · Hemoglobin · Creatinine

Hämoglobin- und Kreatininwerte als prognostische Outcome-Faktoren nach simultaner Radiochemotherapie lokal fortgeschrittener Kopf-Hals-Tumoren

Sekundäre Ergebnisse von 2 randomisierten europäischen Phase-III-Studien (ARO95-06, SAKK 10/94)

Zusammenfassung

Hintergrund Untersucht werden sollte der Einfluss von Baseline-Laborwerten auf das Outcome der Behandlung von Patienten mit fortgeschrittenen Kopf-Hals-Tumoren.
Methoden Daten der randomisierten Studien ARO 95 -06 ($n = 384$) und SAKK 10 /94 ($n = 224$) wurden gepoolt, die Gesamtzahl von 608 Patienten wurde untersucht. Der Einfluss der prätherapeutischen Hämoglobin(Hb)- und Kreatininwerte auf das lokoregionäre rezidivfreien Überleben (LRRFS), das fernmetastasenfreie Überleben (DMFS), das krebsspezifische Überleben (CSS) und das Gesamtüberleben (OS) wurde unter Verwendung uni- und multivariabler Cox-Regressionsmodelle untersucht.
Ergebnisse Insgesamt waren 580 und 564 Patienten mit Hb- und Kreatininwerten in der gepoolten Analyse verfügbar. Univariate Analysen zeigten eine signifikante Assoziation von niedrigen Baseline-Hb-Werten mit vermindertem LRRFS, DMFS, CSS und OS. Dieser Effekt blieb signifikant für das OS, wenn beide Behandlungsarme einzeln untersucht wurden. Höhere Baseline-Kreatininwerte waren mit einem verbesserten OS in der gepoolten Analyse assoziiert. Interessanterweise schien der prognostische Wert des Baseline-Kreatinin auf die Subgruppe der 284 mit simultaner Radiochemotherapie (RCT) behandelten Patienten limitiert zu sein. Nach multivariabler Analyse blieb ein niedriger Baseline-Hämoglobinwert mit einem verminderten OS assoziiert, sowohl bei Patienten mit simultaner RCT als auch bei alleiniger Bestrahlung (HR 0,79, 95 %-KI 0,66–0,94, $p = 0,009$ bzw. HR 0,67, 95 %-KI 0,58–0,78, $p < 0,001$). Ein erhöhter Baseline-Kreatininwert blieb signifikant assoziiert mit einem verbesserten OS bei Patienten mit simultaner RCT (HR 0,79, 95 %-KI 0,69–0,92, $p = 0,002$), aber nicht im Rahmen der alleinigen Bestrahlung.
Schlussfolgerung Es bestätigte sich ein Zusammenhang zwischen niedrigen Baseline-Hämoglobinwerten und unterlegenem Outcome. Der Baseline-Kreatininwert wurde als neuer prognostischer Faktor für die Behandlungsergebnisse der kombinierten RCT bei fortgeschrittenen Kopf-Hals-Tumoren eingeführt.

Schlüsselwörter Kopf-Hals-Plattenepithelkarzinome · Radiotherapie · Chemotherapie · Hämoglobin · Kreatinin

Background

Definitive radiation therapy (RT) usually administered with concurrent platinum-based chemotherapy is one recommended type of treatment for patients with locoregionally advanced squamous cell head and neck cancer (HNSCC) who desire organ preservation, and for those who have surgically unresectable disease [1, 2].

Altered-fractionation RT schedules, including accelerated RT and hyperfractionation, have been investigated to overcome accelerated repopulation and to safely escalate the dose, respectively. Dose-escalated hyperfractionation regimens appear to improve both local control and overall survival (OS) when compared with conventional fractionation RT when given without concurrent chemotherapy. Accelerated fractionation improves locoregional recurrence-free survival (LRRFS), but its effect on OS is less clear [3, 4].

Concomitant chemotherapy has been described to improve OS as compared to RT alone [2, 5, 6]. However, despite combined treatment, prognosis for patients who present with locally advanced (stage III or IV) disease is

poor. The Surveillance, Epidemiology and End Results (SEER) Cancer Statistics review for the years 1975–2007 reports a 5-year relative survival for locally advanced oral cavity and oropharyngeal cancer of 55 %, in contrast to 83 %for early stage disease [7].

For patients with oropharyngeal HNSCC, favourable prognosis is associated with the proof of HPV positivity, both for primary as well as for post-OP radiochemotherapy [8]. For patients with locoregionally advanced oropharyngeal cancer, HPV is associated with long-term local control rates of approximately 80 % in the primary situation [9] and of almost 100 % in the post-OP situation.

Combined chemoradiation has been described to be associated with increased toxicity, which may have a more adverse effect on survival, function and quality of life than has been previously recognized [10]. Thus, every effort should be made to identify predictors for treatment outcomes to be able to escalate or de-escalate treatment intensity for certain subgroups of patients to improve cancer control and to decrease late toxicity.

Methods and patients

The data of the two randomized trials ARO 95/06 and SAKK 10/94 were pooled.

ARO 95/06

In a multicentric, prospective randomized trial on 384 patients with locally advanced HNSCC who were randomized to hyperfractionated accelerated RT with 77.6 Gy (HART) or HART with 70.6 Gy combined with 5-fluorouracil (5-FU) 600 mg/m² as continuous infusion during days 1–5 and mitomycin C (MMC) 10 mg/m² as a single intravenous bolus injection on days 5 and 36, respectively (C-HART). The primary endpoint was locoregional control (LRC). Secondary endpoints were OS, cancer-specific survival (CSS), late treatment-related toxicity, and quality of life.

A creatinine of >1.5 mg/dl or a creatinine clearance ≤80 ml/min was an exclusion criterion for this trial. The long-term follow-up results were recently published with a median follow-up of 8.7 years [5]. The trial was registered with the German Cancer Society (ARO 95/06).

SAKK 10/94

In a multicentric, prospective randomized trial of 224 patients with locally advanced HNSCC who were randomized to receive either hyperfractionated RT alone (median total dose, 74.4 Gy; 1.2 Gy twice daily; 5 days per week) or the same RT combined with two cycles of cisplatin (20 mg/m² for 5 consecutive days during weeks 1 and 5). The primary endpoint was the time to any treatment failure; secondary endpoints were LRRFS, distant metastasis-free survival (DMFS), OS, and late toxicity assessed according to Radiation Therapy Oncology Group (RTOG) criteria. A creatinine clearance ≥60 ml/min was required for participation in this trial. The long-term follow-up results were recently published with a median follow-up of 9.5 years [6]. The trial was registered at the National Institutes of Health (www.clinicaltrials.gov; identifier number: NCT00002654).

Both trials were approved by the local ethics committees of all participating centers and have therefore been conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The pooled total sample size was 608 patients. Baseline laboratory values available for analysis in both trials were haemoglobin (continuous variable, n = 580) and creatinine (continuous variable, n = 564). Note that due to the inclusion/exclusion criteria of the two trials the creatinine values of analyzed patients were within normal limits. All patients for which the respective variables were available were included in the analyses.

The pooled analysis was performed for the endpoints OS, CSS, LRRFS and DMFS. All time-to-event endpoints were calculated from the date of randomization. Locoregional failure was defined as local or nodal progression or recurrence and/or death as a result of tumour. Diagnosis of distant metastasis and death as a result of tumour were considered as events for DMFS. For CSS only death as a result of tumour was counted as an event. The influence of the baseline laboratory values on the time-to-event endpoints was assessed in the pooled data set using univariable Cox regression models with trial as random effect as well as by trial and by treatment arm separately using univariable Cox regression models. Furthermore, multivariable Cox regression models with backward selection were applied by treatment arm. In addition to the baseline haemoglobin and creatinine values, the following clinical and pathological variables were considered as covariates: gender (female vs. male), performance status (WHO grade 0 vs. grade 1–2), primary tumour site (other sites vs. hypopharynx), tumour classification (cT1-2 vs. cT3-4), nodal classification (cN0-1 vs. cN2-3), and age as these were potentially influencing factors of the laboratory values (age and gender) or were previously identified as independent predictors of treatment outcome (performance status, primary tumour site, tumour classification and nodal classification) [5, 6]. Baseline haemoglobin and creatinine were used as continuous variables for all analyses. To obtain more interpretable results, the values were normalized by their interquartile range (IQR). The association between patient characteristics and baseline creatinine was investi-

Table 1 Patient characteristics

Characteristics	SAKK 10/94 (n = 224) No. of patients	%	ARO 95/06 (n = 384) No. of patients	%
Age (years)				
Median	55		55	
Range	(34–74)		(33–71)	
Sex				
Male	190	85	322	84
Female	34	15	62	16
Site				
Oral cavitiy	17	8	32	8
Oropharynx	118	53	228	59
Hypopharynx	55	24	124	32
Larynx	33	15	0	0
Tumour classification[a]				
cT1	4	2	6	2
cT2	37	17	29	8
cT3	101	45	72	19
cT4	81	36	275	72
Nodal classification[a]				
cN0	59	27	20	5
cN1	36	16	35	9
cN2	111	50	272	71
cN3	17	8	57	15
AJCC stage				
II	5	2	0	0
III	64	29	23	6
IV	154	69	361	94
WHO performance status				
0	125	56	252	68
1	90	40	115	31
2	8	4	1	0
Haemoglobin (g/dl)				
n	223		357	
Median	14.1		13.9	
Range	8.2–17		8.1–17.3	
Creatinine (µmol/l)				
n	219		345	
Median	80		70	
Range	29–112		29–134	

[a]Tumour–node–metastasis system classification of malignant tumours, International Union Against Cancer 4th edition #American Joint Committee for Staging of Cancer, 5th edition

gated using the Pearson correlation coefficient for age and weight, the Wilcoxon rank sum test for gender and the Kruskal–Wallis test for performance status.

No adjustment for multiple testing was applied and analyses were exploratory and hypothesis generating because they were retrospectively performed using trials which were not planned for the respective analyses. The significance level was set at 0.05 for all analyses. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics for the trials were summarized in Table 1.

A total of 580 patients were available with baseline haemoglobin values in the pooled analysis. Univariable analyses revealed that lower baseline haemoglobin values were significantly associated with decreased LRRFS (hazard ratio [HR] 0.85, 95 % confidence interval [CI] 0.74–0.96, p = 0.01), decreased DMFS (HR 0.82, 95 % CI 0.70–0.96, p = 0.01), decreased CSS (HR 0.74, 95 % CI 0.64–0.86, $p < 0.001$) and decreased OS (HR 0.76, 95 % CI 0.68–0.86, $p < 0.001$; Table 2). This effect remained significant for OS when the treatment arms (RT alone vs. chemoradiation) were analyzed separately (data not shown).

A total of 564 patients were available with baseline creatinine values. There was only a weak correlation between baseline creatinine and patients age and weight (supplementary Figures 1 and 2). Baseline creatinine was significantly higher in men ($p < 0.001$), whereas no significant association with performance status was detected (p = 0.2). Higher baseline creatinine was associated with improved OS in the pooled analysis (HR 0.88, 95 % CI 0.79–0.99, p = 0.03), while other endpoints were not significantly associated with baseline creatinine in the pooled analysis (Table 3).

Interestingly, the prognostic value of baseline creatinine appeared to be limited to the subgroup of 284 patients who were treated with chemoradiation as compared to patients treated with RT alone (Table 4).

Baseline creatinine clearance was calculated using the Cockcroft–Gault formula for 503 patients (SAKK 10/94: 219, ARO 95/06: 284), for the rest of the patients the baseline weight was not available and thus creatinine clearance could not be calculated. For none of the endpoints a significant association with baseline creatinine clearance could be shown, neither in the pooled analysis nor by treatment or by trial (supplementary Tables 1, 2, 3 and 4).

In the multivariable Cox regression model lower baseline haemoglobin remained associated with decreased OS both in the patients who received chemoradiation (HR 0.79, 95 % CI 0.66–0.94, p = 0.009; Table 5) and in those patients who underwent RT alone (HR 0.67, 95 % CI 0.58–0.78, $p < 0.001$; Table 6). However, increased baseline creatinine remained significantly associated with improved OS in patients who underwent chemoradiation (HR 0.79, 95 % CI 0.69–0.92, p = 0.002; Table 5) but not in those patients who underwent RT alone (Table 6).

Table 2 Univariable Cox regression models for the association of baseline haemoglobin and treatment outcome

	SAKK 10/94 (n = 223)		ARO 95-06 (n = 357)		Pooled analysis (n = 580)	
Variable	HR[a] (95 % CI)	p-value	HR[a] (95 % CI)	p-value	HR[a] (95 % CI)	p-value
OS (years)	0.84 (0.70, 1.02)	0.08	0.73 (0.63, 0.86)	<0.001	0.76 (0.68, 0.86)	<0.001
CSS (years)	0.86 (0.66, 1.11)	0.2	0.72 (0.59, 0.87)	<0.001	0.74 (0.64, 0.86)	<0.001
LRRFS (years)	0.82 (0.66, 1.02)	0.07	0.81 (0.66, 0.98)	0.03	0.85 (0.74, 0.96)	0.01
DMFS (years)	0.82 (0.64, 1.06)	0.1	0.75 (0.59, 0.96)	0.02	0.82 (0.7, 0.96)	0.01

OS overall survival, *CSS* cancer-specific survival, *LRFFS* locoregional failure-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval
[a]IQR normalized for easier interpretation

Table 3 Univariable Cox regression models for the association of baseline creatinine and treatment outcome

	SAKK 10/94 (n = 219)		ARO 95-06 (n = 345)		Pooled analysis (n = 564)	
Variable	HR[a] (95 % CI)	p-value	HR[a] (95 % CI)	p-value	HR[a] (95 % CI)	p-value
OS (years)	0.87 (0.73, 1.04)	0.1	0.92 (0.79, 1.08)	0.3	0.88 (0.79, 0.99)	0.03
CSS (years)	1.05 (0.92, 1.21)	0.4	0.81 (0.66, 0.98)	0.03	0.90 (0.78, 1.04)	0.2
LRRFS (years)	1.06 (0.95, 1.17)	0.3	0.82 (0.67, 1.00)	0.05	0.97 (0.88, 1.08)	0.6
DMFS (years)	1.05 (0.91, 1.20)	0.5	0.82 (0.64, 1.04)	0.1	0.96 (0.85, 1.09)	0.6

OS overall survival, *CSS* cancer-specific survival, *LRRFS* locoregional recurrence-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval
[a]IQR normalized for easier interpretation

Table 4 Univariable Cox regression models for the association of baseline creatinine and treatment by treatment arm

		SAKK 10/94 (n = 219)			ARO 95-06 (n = 345)			Pooled analysis (n = 564)		
Variable		CRT (n = 110)	RT (n = 109)	Interaction[b]	CRT (n = 174)	RT (n = 171)	Interaction[b]	CRT (n = 284)	RT (n = 280)	Interaction[b]
OS (years)	HR[a] (95 % CI)	0.61 (0.49, 0.77)	1.07 (0.96, 1.18)		0.92 (0.75, 1.13)	0.92 (0.73, 1.15)		0.75 (0.66, 0.85)	1.01 (0.89, 1.14)	
	p-value	<0.001	0.2	0.03	0.4	0.5	0.04	<0.001	0.9	<0.001
CSS (years)	HR[a] (95 % CI)	0.64 (0.46, 0.88)	1.11 (1.02, 1.21)		0.79 (0.60, 1.04)	0.80 (0.61, 1.06)		0.70 (0.59, 0.82)	1.05 (0.94, 1.18)	
	p-value	0.006	0.002	0.01	0.01	0.1	0.009	<0.001	0.4	<0.001
LRRFS (years)	HR[a] (95 % CI)	0.76 (0.57, 1.01)	1.08 (1.00, 1.17)		0.71 (0.53, 0.96)	0.91 (0.68, 1.20)		0.76 (0.63, 0.93)	1.04 (0.95, 1.14)	
	p-value	0.06	0.04	0.04	0.03	0.5	<0.001	0.006	0.4	<0.001
DMFS (years)	HR[a] (95 % CI)	0.61 (0.45, 0.85)	1.11 (1.02, 1.21)		0.77 (0.56, 1.07)	0.88 (0.61, 1.28)		0.75 (0.62, 0.9)	1.07 (1, 1.16)	
	p-value	0.003	0.01	0.007	0.1	0.5	0.6	0.002	0.07	0.01

CRT chemoradiation therapy, *RT* radiation therapy, *OS* overall survival, *CSS* cancer-specific survival, *LRFFS* locoregional recurrence-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval
[a]IQR normalized for easier interpretation
[b]Likelihood-ratio test for the interaction between treatment arm and creatinine

Discussion and conclusion

This analysis confirmed the notion that low baseline haemoglobin is an adverse prognostic factor in patients with locally advanced HNSCC who undergo chemoradiation or RT alone. Interestingly, we also found that increased baseline creatinine (with all patients having creatinine values within normal limits) appeared to be associated with improved OS in those patients who underwent chemoradiation but not in those who underwent RT alone.

Anaemia commonly occurs in patients with HNSCC and may be caused by a number of factors, including comorbid illness, intraoperative blood loss, toxicity from chemother-

Table 5 Treatment outcome analysis following chemoradiation therapy, pooled analysis of SAKK 10/94 and ARO 95-06 trials

Variable	Multivariable Cox regression analysis, hazard ratio[a] (95 % CI) (*p*-value)			
	OS	CSS	LRRFS	DMFS
Full model				
Gender: male vs. female	1.53 (0.99, 2.35) (0.05)	1.36 (0.8, 2.31) (0.3)	1.72 (0.98, 3.04) (0.06)	1.62 (0.87, 3.02) (0.1)
Performance status: 1+2 vs. 0	1.39 (1.06, 1.83) (0.02)	1.42 (1, 2.03) (0.05)	1.26 (0.89, 1.8) (0.2)	1.57 (1.06, 2.33) (0.02)
Site: hypopharynx vs. other sites	0.92 (0.67, 1.26) (0.6)	0.82 (0.55, 1.22) (0.3)	0.82 (0.55, 1.21) (0.3)	0.63 (0.41, 0.97) (0.04)
Tumour classification: cT3-4 vs. cT1-2	1.09 (0.68, 1.73) (0.7)	1.21 (0.65, 2.27) (0.6)	1.42 (0.79, 2.58) (0.2)	1.08 (0.55, 2.12) (0.8)
Nodal classification: cN2-3 vs. cN0-1	1.27 (0.9, 1.79) (0.2)	1.39 (0.87, 2.23) (0.2)	1.65 (1.05, 2.6) (0.03)	1.09 (0.67, 1.8) (0.7)
Age	1 (0.98, 1.02) (0.9)	0.99 (0.97, 1.01) (0.3)	0.99 (0.97, 1.01) (0.2)	1 (0.97, 1.02) (0.9)
Haemoglobin at baseline	0.8 (0.67, 0.96) (0.01)	0.74 (0.59, 0.93) (0.01)	0.81 (0.64, 1.01) (0.06)	0.76 (0.59, 0.99) (0.04)
Creatinine at baseline	0.81 (0.7, 0.94) (0.005)	0.8 (0.66, 0.98) (0.03)	0.79 (0.63, 0.98) (0.04)	0.72 (0.57, 0.91) (0.006)
After backward selection (with level 0.05)				
Gender: male vs. female	1.55 (1.01, 2.37) (0.05)			1.66 (1.14, 2.4) (0.007)
Performance status: 1+2 vs. 0	1.39 (1.07, 1.81) (0.01)			
Site: other sites vs. hypopharynx				0.64 (0.43, 0.97) (0.04)
Tumour classification: cT3-4 vs. cT1-2				
Nodal classification: cN2-3 vs. cN0-1			1.68 (1.08, 2.62) (0.02)	
Age				
Haemoglobin at baseline	0.79 (0.66, 0.94) (0.009)	0.77 (0.62, 0.95) (0.02)		
Creatinine at baseline	0.79 (0.69, 0.92) (0.002)	0.77 (0.64, 0.93) (0.007)	0.77 (0.63, 0.94) (0.01)	0.73 (0.61, 0.87) (<0.001)

CRT chemoradiation therapy, *RT* radiation therapy, *OS* overall survival, *CSS* cancer-specific survival, *LRFFS* locoregional recurrence-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval

[a]IQR normalized for easier interpretation

apy and/or RT, and malignancy-associated anaemia of chronic disease.

Anaemia is commonly thought to enhance radioresistance via enhancing tumour hypoxia and has been described to be associated with decreased cancer control and OS in several reports [11, 12]. The impact of anaemia on treatment outcome in patients with squamous cell carcinoma of the larynx and pharynx was confirmed in the DAHANCA 5–85 study where the use of the radiosensitizer nimorazole in association with RT was shown to significantly improve LRC and CSS [13] and multivariable analysis in the study of Denis et al. [14] revealed low haemoglobin level as the most adverse factor for LRRFS, DMFS and OS. The finding however that anaemia correlates with inferior LRC among patients treated with surgery alone suggests that anaemia may influence outcome in head and neck cancer patients also independent of its influence on hypoxic radioresistance [15].

Attempts were made to overcome the negative effect of low baseline haemoglobin. In the DAHANCA 5 and 7 protocols including a total of almost 1200 head and neck cancer patients, low haemoglobin patients were subrandomized to red blood cell transfusion or no transfusion. These studies showed that transfusions to patients with haemoglobin level below 13 g/dl in females and 14.5 g/dl in males, raised the haemoglobin levels and brought these patients into the high haemoglobin group. However there was no benefit of transfusion on RT outcome with respect to LRC, CSS or OS [12]. Moreover, the role of erythropoiesis-stimulating agents (ESAs) have been investigated in several trials and a 2012 Cochrane review of 91 trials with 20,102 participants came to the conclusion that ESAs increase mortality during active therapy (on-study mortality, HR 1.17, 95 % CI 1.06–1.29), and modest evidence that they increase overall mortality (HR 1.05, 95 % CI 1.00–1.11) [16].

Little is known regarding the prognostic effect of baseline creatinine in patients undergoing chemoradiation. We screened the literature but did however not identify any report describing this relationship. We are not aware of any study setting the efficacy of chemotherapy given simultane-

Table 6 Treatment outcome analysis following radiation therapy, pooled analysis of SAKK 10/94 and ARO 95-06 trials

Variable	Multivariable Cox regression analysis, hazard ratio[a] (95 % CI) (*p*-value)			
	OS	CSS	LRRFS	DMFS
Full model				
Gender: male vs. female	1.97 (1.34, 2.9) (<0.001)	1.81 (1.14, 2.87) (0.01)	1.16 (0.76, 1.76) (0.5)	1.85 (1.06, 3.24) (0.03)
Performance status: 1+2 vs. 0	1.32 (1.02, 1.7) (0.03)	1.47 (1.08, 1.99) (0.01)	1.56 (1.16, 2.1) (0.003)	1.39 (0.96, 1.99) (0.08)
Site: hypopharynx vs. other sites	1.03 (0.77, 1.37) (0.8)	0.91 (0.65, 1.29) (0.6)	1.05 (0.74, 1.48) (0.8)	0.81 (0.53, 1.22) (0.3)
Tumour classification: cT3-4 vs. cT1-2	1.36 (0.9, 2.07) (0.2)	1.38 (0.83, 2.3) (0.2)	1.52 (0.9, 2.56) (0.1)	2.19 (1.12, 4.27) (0.02)
Nodal classification: cN2-3 vs. cN0-1	1.3 (0.95, 1.8) (0.1)	1.48 (1, 2.2) (0.05)	1.18 (0.82, 1.71) (0.4)	2.46 (1.49, 4.06) (<0.001)
Age	1 (0.98, 1.02) (0.9)	0.99 (0.97, 1.01) (0.5)	0.98 (0.96, 1) (0.04)	0.99 (0.97, 1.02) (0.5)
Haemoglobin at baseline	0.7 (0.59, 0.82) (<0.001)	0.73 (0.6, 0.87) (<0.001)	0.83 (0.7, 1) (0.05)	0.73 (0.55, 0.97) (0.03)
Creatinine at baseline	0.99 (0.87, 1.13) (0.9)	1.03 (0.92, 1.16) (0.6)	1.07 (1, 1.14) (0.07)	1.04 (0.96, 1.13) (0.3)
After backward selection (with level 0.05)				
Gender: male vs. female	1.94 (1.33, 2.84) (<0.001)	1.85 (1.17, 2.91) (0.008)		1.94 (1.11, 3.37) (0.02)
Performance status: 1+2 vs. 0	1.29 (1, 1.66) (0.05)	1.45 (1.07, 1.96) (0.02)	1.57 (1.17, 2.09) (0.002)	
Site: other sites vs. hypopharynx				
Tumour classification: cT3-4 vs. cT1-2				2.18 (1.13, 4.2) (0.02)
Nodal classification: cN2-3 vs. cN0-1		1.49 (1.01, 2.2) (0.04)		2.52 (1.54, 4.13) (<0.001)
Age			0.98 (0.96, 1) (0.03)	
Haemoglobin at baseline	0.67 (0.58, 0.78) (<0.001)	0.73 (0.61, 0.88) (<0.001)		0.73 (0.55, 0.96) (0.02)
Creatinine at baseline				

CRT chemoradiation therapy, *RT* radiation therapy, *OS* overall survival, *CSS* cancer-specific survival, *LRFFS* locoregional recurrence-free survival, *DMFS* distant metastasis-free survival, *HR* hazard ratio, *CI* confidence interval

[a]IQR normalized for easier interpretation

ous to RT into the context of kidney function. Interestingly our data suggest that impaired kidney function, although in the range of values allowing application of chemotherapy in these trials, is associated with better prognosis in those patients receiving chemoradiation but not in the patients receiving RT alone. As the kidneys are the major elimination pathway for cisplatin and to a lower extent for mitomycin our data suggest that renal impairment may result in delayed drug metabolism and excretion, resulting in increased systemic effects of these antineoplastic drugs.

However, calculation of the creatinine clearance (fewer patients available due to missing weight in several patients) did not reveal any associations with treatment outcome suggesting that baseline creatinine might only be a surrogate marker for patient condition (e. g. weight, muscle mass, training status) and not directly linked to kidney function. However, there was only a weak correlation between baseline creatinine and weight (supplementary Figure 2), given that weight represents both muscle and fat mass. The reason for the identified association between baseline creatinine values and outcome parameters remains thus to be elucidated.

Besides the results for the mentioned laboratory values our analysis revealed that gender, age, performance status, tumour site, tumour classification and nodal classification were significantly associated with outcome after chemoradiation or RT alone, however, most of these associations have been described before [5, 6].

A limitation of our analysis is, however, that there are several other factors with known influence on kidney function as other diseases, co-medication, fluid restriction etc., which were not available for analysis in the two analyzed trials [17, 18]. Another limitation is that baseline lab values were not available for analysis in several of the patients.

Also it has to be acknowledged that this was an unplanned retrospective analysis of the two trials and the data is therefore of exploratory nature.

It remains currently unclear which interventions might be based in clinical practice on haemoglobin and creatinine assessment. As red blood cell transfusions or ESAs do not improve the prognosis of patients with low baseline haemoglobin, low baseline haemoglobin at present remains a prognostic factor for poor outcome in patients with locally advanced HNSCC. Nevertheless, this parameter may potentially be important as one of several parameters in prognostic panels for selection of patients for intensified treatment, e. g. radiation dose-escalation. Regarding baseline creatinine it is necessary to confirm this parameter as a prognostic parameter in currently ongoing prospective trials for patients undergoing chemoradiation, and if confirmed, to characterize this association in more detail.

Conclusion

Our data from a secondary joint analysis of two randomized trials confirm published knowledge regarding baseline haemoglobin as a prognostic parameter and introduce baseline creatinine as a novel predictor of outcome after chemoradiation for locally advanced HNSCC.

Availability of data and materials The databases for the trials are managed by the SAKK coordinating center (SAKK 10/94) or the Department of Radiation Oncology, Charité Universitätsmedizin Berlin (ARO 95-06) and are not publicly available.

Trial registration ARO 95-06 was registered with the German Cancer Society and SAKK 10/94 was registered at the National Institutes of Health (www.clinicaltrials.gov; identifier number: NCT00002654)

Acknowledgements For the ARO 95-06 trial the following contributors enrolled patients into the trial without meeting the criteria for authorship: W. Hinkelbein, S. Koswig, P. Wust, H. Frommhold, J. Dunst, M.-L. Sautter-Bihl, M. Fritsche and S. Blass were responsible for data collection and follow-up.

Funding The ARO 95-06 trial was supported by Grant 70-1693 of the Deutsche Krebshilfe e. V.

The SAKK 10/94 trial was supported by the Swiss State Secretariat for Education, Research and Innovation (SERI).

Compliance with ethical guidelines

Conflict of interest P Ghadjar, C. Pöttgen, D. Joos, S Hayoz, M. Baumann, S. Bodis, W. Budach, G. Studer, C. Stromberger, F. Zimmermann, D. Kaul, L. Plasswilm, H. Olze, J Bernier, P. Wust, D.M. Aebersold and V. Budach declare that they have no competing interests.

The accompanying manuscript does not include studies on humans or animals performed by any of the authors.

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