

Acute Arterial Hemorrhage Following Radiotherapy of Oropharyngeal Squamous Cell Carcinoma

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Background and Purpose: Vascular erosion is a rare but life-threatening complication after radiotherapy. The authors report on acute arterial bleeding and its therapy following radiotherapy of oropharyngeal tumors.

Patients and Methods: Ten patients with oropharyngeal squamous cell carcinoma of any stage developed foudroyant acute arterial hemorrhage 3–46 months (14.4 ± 5.1 months) after primary (5/10) or adjuvant radio(chemo)therapy (R[C]T).

Results: All patients had a history of recurrent minor bleeding episodes and showed deep mucosal ulcerations also outside the primary tumor region. A life-threatening arterial hemorrhage appeared in the area of these mucosal defects in the pharyngeal region. Affected vessels were the common carotid artery as well as the internal and the external portion with branches like the ascending pharyngeal and superior thyroid arteries. Treatment consisted of emergency intubation or tracheotomy followed by exposure and package of the pharynx and surgical ligation and/or embolization. 6/10 patients (all hospitalized) survived the episode, however, lethal outcome in 4/10 patients (outpatients) was related to asphyxia as a result of blood aspiration or exsanguination. None of the patients revealed evidence of persistent or recurrent tumor disease as proven by biopsy/autopsy and imaging technique.

Conclusion: Vascular erosion following primary or adjuvant R(C)T represents a rare and potentially life-threatening complication requiring immediate emergency treatment involving head and neck surgeons, anesthesiologists and neuroradiologists. For patients with oropharyngeal neoplasms treated by R(C)T and showing recurrent bleeding episodes and mucosal ulceration particularly after the acute treatment phase, hospitalization with prophylactic surgical ligation or embolization of affected arteries is recommended.

Key Words: Hemorrhage · Radiotherapy · Head-neck cancer · Ligation · Embolization

Strahlenther Onkol 2010;186:269–73
DOI 10.1007/s00066-010-2114-5

Fatale Arrosionsblutung nach Bestrahlung oropharyngealer Plattenepithelkarzinome

Hintergrund und Ziel: Schädigungen von Blutgefäßen stellen eine seltene, jedoch potentiell lebensbedrohliche Komplikation nach Strahlentherapie dar. Die Autoren berichten über akute arterielle Blutungen und deren Therapie nach Strahlentherapie von oropharyngealen Tumoren.

Patienten und Methodik: Zehn Patienten mit einem oropharyngealen Plattenepithelkarzinom jeglichen Tumorstadiums entwickelten 3–46 Monate ($14,4 \pm 5,1$ Monate) nach primärer (5/10) oder adjuvanter Radio(chemo)therapie (R[C]T) eine akute arterielle Blutung (Tabelle 1).

Ergebnisse: Alle Patienten zeigten in ihrer Vorgeschichte kleinere Blutungsepisoden und litten unter tiefen Schleimhautulcerationen im Pharynx auch außerhalb der Primärtumorregion (Abbildung 1). Die lebensbedrohlichen Blutungen traten im Bereich dieser Schleimhautdefekte auf. Betroffene Gefäße waren die Arteriae carotis communis, carotis interna und carotis externa mit ihren Ästen, Arteria pharyngea ascendens und Arteria thyroidea superior. Die Therapie umfasste die notfallmäßige Intubation oder Tracheotomie und Tamponade des Rachens, gefolgt entweder von einer Ligatur (Abbildung 2) und/oder Embolisation des

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Received: December 12, 2009; accepted: February 16, 2010
Published Online: April 26, 2010

betroffenen Gefäßes. 6/10 Patienten überlebten dieses Ereignis, 4/10 Patienten verstarben vor Erreichen der Klinik infolge des hohen Blutverlusts oder Aspiration. Keiner der Patienten zeigte zum Zeitpunkt der Blutung bildmorphologisch oder histologisch einen Residual- oder Rezidivtumor.

Schlussfolgerung: Gefäßschädigungen infolge primärer oder adjuvanter R(C)T stellen eine potentiell lebensbedrohliche Komplikation dar, die einer unmittelbaren notfallmäßigen interdisziplinären Behandlung durch Kopf-Hals-Chirurgen, Anästhesisten und Neuroradiologen bedarf. Bei Patienten mit oropharyngealen Karzinomen, die nach einer R(C)T unter wiederkehrenden pharyngealen Blutungsepisoden und Schleimhautulcerationen leiden, sollte eine stationäre Überwachung mit einer eventuellen prophylaktischen Unterbindung oder einem neuroradiologisch-interventionellen Verschluss (Abbildung 3) der betroffenen Gefäße in Erwägung gezogen werden.

Schlüsselwörter: Arrosionsblutung · Strahlentherapie · Kopf-Hals-Tumoren · Ligatur · Embolisation

Introduction

Head and neck squamous cell carcinomas (HNSCC) are among the most frequent malignancies in the upper aerodigestive tract. Radio(chemo)therapy (R[C]T), in several combinations [16], alone or together with surgery is an established method in treatment protocols of HNSCC [11].

Common side effects of R(C)T are erythema, erosion and ulceration of the skin and mucosa, xerostomia, interstitial lymphedema, fibrosis of the soft tissue, and, in severe cases, necrosis of bone or cartilage [8]. It is discussed, that radiation-induced late effects like chronic inflammation, organ dysfunction, fibrosis and necrosis are driven, in part, by chronic oxidative stress [21].

Furthermore, vascular alterations are occasionally observed. Vascular changes contain premature atherosclerosis with stenosis [14], adventitial fibrosis, and weakening of the arterial wall caused by obliteration of the vasa vasorum [4, 13]. However, acute rupture of irradiated large vessels is a rare, but life-threatening complication [15]. Most of the vascular erosions of cervical arteries appear in patients with complications like recurrent tumors, wound infections, or pharyngocutaneous fistulas [1, 6, 7, 19].

Here, we present a series of ten patients with oropharyngeal carcinomas suffering from acute and life-threatening arterial bleeding after primary or adjuvant R(C)T without evidence of above-described comorbidity or residual as well as recurrent tumor burden.

Patients and Methods

Patients' data were collected during a 4.5-year period and involved individuals affected by oropharyngeal squamous cell carcinoma who developed acute arterial hemorrhage after primary or adjuvant R(C)T. Only patients, who revealed no evidence of persistent or recurrent tumor disease as proven by histology/autopsy and imaging technique at the time of acute hemorrhage were included.

Charts were reviewed for age, gender, tumor localization and size, oncologic therapy, timing between end of irradiation and appearance of acute bleeding, localization of bleeding, and treatment as well as outcome (Table 1).

Ten patients, nine men and one woman with a mean age of 56.5 ± 3.3 years (range 42–70 years) were included. All suffered from an oropharyngeal squamous cell carcinoma, classified T1 through T4, most of them with cervical lymph node metastasis (8/10 patients), all without distant metastasis. Four patients were treated with primary R(C)T (patients 2, 4, 6, and 8). One of them (patient 2), with an N2c cervical lymph node metastasis, received a salvage neck dissection due to persistent cervical nodes 9 months after irradiation. Four patients achieved adjuvant postoperative RT (patients 5 and 9) or RCT (patients 7 and 10). One patient with a T1 carcinoma of the right side (patient 1) underwent initial surgery. 4 years later he developed a T3 second primary at the left oropharyngeal side, which was treated with (primary) RCT. One patient with a T2 N2c oropharynx carcinoma (patient 3) was first treated with surgery in combination with postoperative RT and hyperthermia. 1 year later when a relapse occurred he achieved again RT. The median cumulative irradiation dose averaged at 72.1 ± 3.1 Gy.

Results

Ten patients developed acute arterial hemorrhage 3–46 months (14.4 ± 5.1 months) after primary or adjuvant R(C)T. In one case the bulb of the common carotid artery (patient 2), in seven patients external branches (patients 1, 3, 4, 5, 6, 9, and 10), and in two individuals the internal trunk (patients 7 and 8) of the carotid artery was affected.

All patients had a history of recurrent episodes of minor pharyngeal bleeding attacks and showed mucosal ulceration of the lateral wall of the pharynx and also outside the primary cancer region (Figure 1).

Four of ten patients died, all of them before arriving at the trauma room, because of exsanguination or asphyxiation related to blood aspiration, due to the long access route up to the clinic. The causative vessel, and the absence of tumor, was identified by autopsy later. The other six patients were hospitalized and emergency treatment comprised, in close cooperation with anesthetists, stabilization of the circulatory system by intravenous application of vasoactive drugs and blood substitution therapy, intubation (2/6) or tracheotomy (4/6) to prevent blood aspiration. This was followed by identification of the bleeding area, and if hemostasis by local measures was

Table 1. Clinicopathologic features of ten patients with oropharyngeal squamous cell carcinoma. F: female; 5-FU: 5-fluorouracil; M: male.**Tabelle 1.** Klinisch-pathologische Parameter der 10 Patienten mit oropharyngealem Plattenepithelkarzinom. F: weiblich; 5-FU: 5-Fluorouracil; M: männlich.

Patient #	Age (years)	Sex	Tumor localization	Therapy	Cumulative irradiation dose (Gy)	Time between end of irradiation and hemorrhage (months)	Localization of bleeding	Treatment/ outcome
1	42	M	T1 N0 M0 right oropharynx	Surgery	74	12	Left external carotid artery	Lethal
			T3 N0 M0 left oropharynx 4 years later	Primary radiochemotherapy: 74 Gy 2 courses of cisplatin		12		
2	48	M	T2 N2c M0 left oropharynx	Primary radiochemotherapy: 74 Gy 2 courses of cisplatin 1 course of 5-FU Surgery	74	46	Left common carotid artery	Ligation of left common carotid artery
			Lymph node metastasis left side 9 months later					
3	48	M	T2 N2c M0 right oropharynx	Surgery Irradiation 66 Gy + hyperthermia	96.6	43	Right ascending pharyngeal artery	Lethal
			Right oropharynx 1 year later	Irradiation 30.6 Gy				
4	66	M	T4 N2c M0 right oropharynx	Primary radiochemotherapy: 74 Gy 2 courses of cisplatin	74	3	Right superior thyroid artery	Ligation of right superior thyroid artery
5	51	M	T2 N2c M0 right oropharynx	Surgery Irradiation 64.8 Gy	64.8	6	Right external carotid artery	Embolization of right external carotid artery
6	69	M	T3 N2c M0 oropharynx	Primary radiochemotherapy: 74 Gy 1 course of cisplatin 1 course of carboplatin	74	8	Tongue base	Local coagulation
7	67	M	T3 N1 M0 left oropharynx	Surgery Irradiation 66 Gy 2 courses of cisplatin	66	4	Left internal carotid artery	Lethal
8	49	M	T4N2cM0 left oropharynx	Primary Radiochemotherapy: 70 Gy 2 courses of cisplatin	70	12	Left internal carotid artery	Lethal
9	70	F	T3 N0 M0 left oropharynx	Surgery (R1) Irradiation 64 Gy	64	5	Left ascending pharyngeal artery	Ligation of left ascending pharyngeal artery
10	55	M	T1 N2b M0 left oropharynx	Surgery Irradiation 64 Gy 2 courses of cisplatin	64	6	Left external carotid artery externa and left ascending pharyngeal artery	Ligation of left external carotid artery and embolization of left ascending pharyngeal artery

not possible, either surgical (5/6) or interventional occlusion of the relevant vessel was performed by a head and neck surgeon and neuroradiologist, respectively.

Only in patient 6 local coagulation of the tongue base was sufficient to arrest the bleeding originating from branches of the lingual artery.

In one patient (patient 5) bleeding was stopped by embolization and in three other patients by ligation of the relevant vessels by surgical exposure (patients 2, 4, and 9; Figure 2). In patient 10 both methods were combined because ligation of the external branches of the carotid artery did not include the ipsilateral ascending pharyngeal artery (caudal and dorsal



Figure 1. Mucosal lesion in the left oropharynx after (curative) primary radiochemotherapy.

Abbildung 1. Schleimhautdefekt im linken Oropharynx nach (kurativer) primärer Radiochemotherapie.

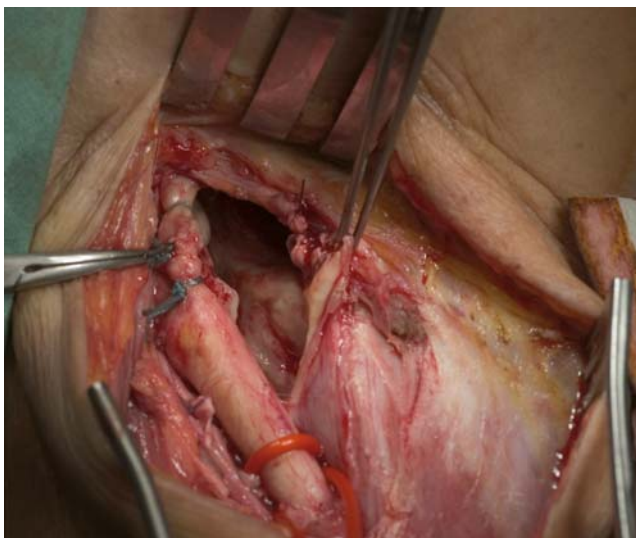


Figure 2. Ligation of the right external carotid artery over a 2 × 4 cm pharyngeal defect after radiochemotherapy.

Abbildung 2. Ligatur der rechten Arteria carotis externa über einem 2 × 4 cm großen Pharynxdefekt nach Radiochemotherapie.

origin) and subsequently led to recurrent bleeding episodes. All successfully treated patients survived without neurologic deficits.

6 months after arterial ligation, patient 9 died of heart failure without a connection to previous therapy or evidence of tumor recurrence. Today, on average 2.98 ± 1.22 years (range 1–5.3 years) after the bleeding complication, the other patients are still alive without any evidence of tumor recurrence.

Discussion

Acute arterial hemorrhage following primary or adjuvant R(C)T is particularly dangerous when located in the upper aerodigestive tract. Airway obstruction, aspiration and subsequent asphyxia may lead to lethal outcome, particularly if the patient is not in hospital [9, 10, 18]. There are various potential reasons for arterial erosions after R(C)T. Principally, an infiltration of a recurrent tumor with destruction of the artery has to be considered. Tumor regression after R(C)T leads to a defect in the vessel wall and hemorrhage during or shortly after completion of the protocol. However, in none of the ten presented patients a tumor was detectable by means of histology/autopsy and imaging technique. Furthermore, the time interval between completion of the RCT and the bleeding seems too long (mean 14.4 ± 5.1 months) for representing a vessel leakage caused by tumor regression.

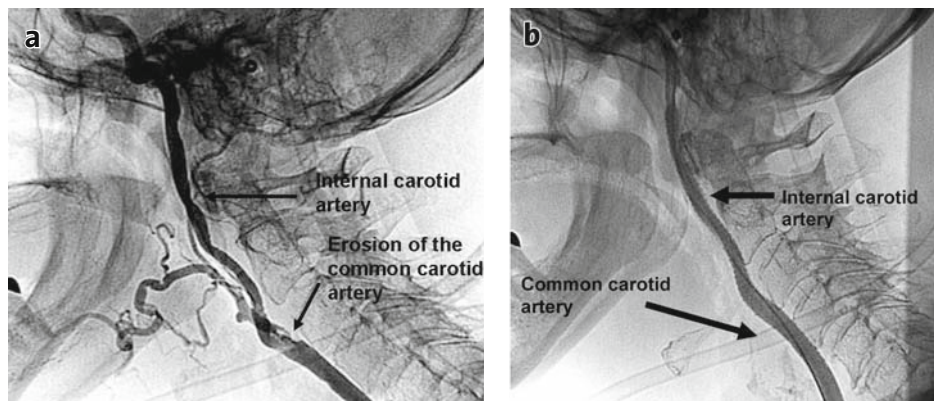
Those late bleedings are most likely caused by long-term effects of irradiation. Radiation-induced vascular changes varied from atherosclerosis to necrotizing vasculitis characterized by fragmentation of the internal elastic lamellae, focal medial necroses or edema and inflammatory infiltration predominantly by polymorphonuclear leukocytes of adventitia, media and intima [8]. These radiation-induced late effects seem to be caused by chronic oxidative stress [21]. Mitigation or treatment of chronic radiation damage has been shown experimentally in multiple organ systems, with different pharmacological agents, like angiotensin-converting enzyme inhibitors, pentoxifylline and superoxide dismutase mimetics, or gene therapeutic strategies [17]. Unfortunately, the mechanistic basis for most of the experimental successes has not been established, and assessment of the utility of these agents for clinical use has been slow. Necrosis of the vascular wall may lead to a rupture of the artery. However, since only ligation and not resection of the bleeding artery was performed in some patients (patients 2, 4, 9, and 10), there is no histopathologic proof of this hypothesis.

Some patients displayed a mucosal defect outside the primary tumor region but inside the radiation field, which argues against vascular erosion by tumor but for a radiation side effect. This was the case in a patient with an oropharyngeal tumor having a late onset of vascular erosion (common carotid artery) at the level of the hypopharynx.

The first-line treatment of acute arterial hemorrhage consists of emergency stabilization of the respiratory and cardiovascular system and cessation of the bleeding by packing the pharynx followed by immediate arterial embolization [5, 12] or surgical ligation [20].

However, interruption of blood flow of the internal carotid artery carries significant risk for cerebral ischemia, which was not the case in our series of patients.

In general, patients with oropharyngeal cancer who received RT and display recurrent minor bleeding attacks as



Figures 3a and 3b. Erosion of the left common carotid artery before (a) and after (b) insertion of a covered stent.

Abbildungen 3a und 3b. Arrosion der linken Arteria carotis communis vor (a) und nach (b) Einlage eines ummantelten Stents.

well as mucosal defects should undergo angiography by an experienced neuroradiologist to detect possible damages to the vascular wall early enough to prevent a life-threatening bleeding. If such a damage is detected, prophylactic therapy like selective endovascular occlusion or surgical ligation of altered arteries or bridging of the damaged vascular part by angiographic insertion of covered stents (Figure 3) has to be considered [2, 3].

Conclusion

Vascular erosion following primary or adjuvant R(C)T represents a rare and potentially life-threatening complication requiring immediate emergency treatment involving head and neck surgeons, anesthesiologists, and neuroradiologists. An improvement in survival rates may be obtained, if prophylactic embolization, ligation or stenting of affected vessels is performed particularly in those individuals who display recurrent bleeding attacks as well as mucosal defects after R(C)T.

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