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RHINOLOGY

Metastatic behaviour of sinonasal adenocarcinomas of the intestinal type (ITAC)

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Abstract The relative frequency of regional lymphogenic versus distant hematogenic metastases was evaluated in 369 patients with sinonasal adenocarcinoma of the intestinal type (ITAC). We assessed the results of neck dissections for a limited number of patients undergoing this surgical intervention. 117 ITAC patients were followed up for at least 5 years. Neck dissections were performed in 18 cases (15 primary and 3 secondary operations), 4 of which revealed carcinoma-positive lymph nodes. Metastases in lymph nodes were also diagnosed clinically in three other patients adding up to a total of seven individuals (6 % of 117) with lymphogenic metastases. In comparison, distant hematogenic metastases were identified in 15.4 % of these 117 patients. In the second group of 252 patients, the occurrence of distant hematogenic metastases and colorectal adenocarcinomas was registered but no formal follow-up procedure was applied. 50 neck dissections were performed in this group, 46 of which exhibited no histological evidence for metastases in lymph nodes, while in 1 case they were carcinoma-positive. Three additional cases showed clinical signs of metastases in regional lymph nodes. Taken together, our observations indicate that regional lymphogenic metastases are rather rare (about 2 %) in patients with sinonasal adenocarcinoma of the intestinal type. Therefore, the surgery of neck dissection appears not advised as routine intervention in these cases. ITAC patients show a normal prevalence of colorectal adenocarcinomas.

Keywords Intestinal type adenocarcinoma · ITAC · Lymph node · Metastasis · Neck dissection · Colorectal adenocarcinoma · Wood dust

Introduction

Sinonasal adenocarcinomas are rare. According to WHO classification from 2005 these tumours are subdivided into adenocarcinomas of the intestinal type (ITAC) and the non-intestinal type (non-ITAC), and adenocarcinomas of the salivary gland type [1]. The present study concentrates on metastatic behaviour of a large number of ITAC in a retrospective evaluation.

ITAC are histologically and immunohistochemically very similar to colorectal adenocarcinomas (CRAC). In view of this fact, it is discussed whether both tumour types share essential signalling pathways that may serve as targets for therapeutic intervention [2, 3]. In this context, it is interesting to investigate whether ITAC and CRAC also share metastatic properties. Specifically, we would like to know whether the lymphogenic metastatic spreading that is dominant in CRAC would also play a major role in ITAC. According to the published data, ITAC possess only very low metastatic potential but display aggressive local growth [4–6]. In contrast to metastases in CRAC, those in ITAC are more frequently haematogenic than lymphogenic. However, so far no or very few data on large scale case studies of these tumours are available. Therefore, it is quite unclear how important the immediate elective neck dissection is for tumour patients [7]. Here, we

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performed a large retrospective investigation to determine the frequency of regional lymphogenic versus distant haematogenic metastases produced by these very rare adenocarcinomas. The unique study was performed on an unusually large collection of material and data from patients with ITAC to obtain statistical information on the question of how sensible and beneficial a neck dissection would be in these cases. The occurrence of distant metastases from ITAC may, in addition to the notorious frequent contribution by CRAC, also add to the likelihood of metastases of the intestinal adenocarcinoma type in liver, skeleton and other locations.

Materials and methods

Histological examination was carried out on formalin-fixed, paraffin-embedded (FFPE) tissue from 447 tumour patients. These samples have been collected on request of the German Professional Trade Association for Wood and Metal. It was confirmed that all workers providing samples had been exposed to wood dust for many years. The specimens fell into two groups. First 117 cases of ITAC from a 4-year period (2000–2003) were subjected to further analysis as part of the retrospective study. From these patients (referred to as "study cases"), we obtained FFPE tumour tissue, complete records of the Trade Association, and data on clinical trials over at least 5 years. The age distribution of these 114 male and 3 female (2.6 %) patients ranged from 39 to 87 years with a mean age of 64.0.

The second group consisted of 330 cancer patients between 2002 and 2013. For these cases, FFPE material was received for histological examination to obtain a reference assessment of the external microscopic diagnoses (referred to as "reference cases"). For these cases, routine reference records of the Trade Association, operation reports, histological findings, coloscopic data in some optional cases, and discharge letters were available. This information was assembled for the purpose of assessing whether or not the tumour would be accepted as occupational disease. The quality and quantity of medically relevant information were very variable. Only in few cases, details on the progression of the disease were known. Based on our histological assessment, there were 252 cases of ITAC and 78 tumours of non-ITAC (23.6 %). The mean age of the patients with ITAC and non-ITAC was 66.8 and 59.0 years, respectively. The ITAC reference group contained eight (2.3 %); the non-ITAC group three (3.9 %) women.

Histological tumour diagnosis in all cases was based on the following stainings and immunohistochemical reactions (APAAP method): haematoxylin–eosin; PAS-Alcian; CK20, DAKO 1:50; CDX2, Biogenex 1:100; CK7, Menarini 1:100; Synaptophysin, DAKO 1:100; p53, DAKO 1:100; MIB1, DAKO 1:100. Additional primary antibodies were used where needed.

Results

Study cases

The tumour categories of the 117 "study cases" was analysed using the clinical, radiological and histopathological data in accordance with the TNM classification 2009, 7th edition [8]. Twelve cases (10.3 %) were assigned to category T1, 60 cases (51.3 %) to category T2, 20 cases (17.1 %) to category T3 and 25 cases (21.4 %) to category T4. Histopathological grading [9] of the study cases resulted in 11 grade-1 tumours (9.4 %), 70 grade-2 carcinomas (59.8 %) and 36 grade-3 cases of the ITAC type (30.8 %).

In 111 of the 117 "study cases" (94.9 %), surgical sinonasal tumour operations were successfully carried out or attempted either exclusively endonasal (24 cases) or by external access (89 cases). In four cases, only a biopsy of the carcinoma was performed due to the advanced inoperable state of the tumours. In 81 cases, radiotherapy was performed (69.2 % of all study cases); 28 of these patients received combined radiochemotherapy.

Neck dissections were performed in 18 of the 117 "study cases" (15.4 %): of 15 primary neck dissections, one patient was node-positive, while three patients with secondary neck dissections carried out 22, 40 and 60 months after the first operation were carcinoma-positive. Three further cases developed metastases in regional lymph nodes over time, resulting in 7 from 117 patients (6 %) with lymph node metastasis at the end of the complete period of disease progression. Four of whom were with and three of whom were without signs of haematogenic metastasis during subsequent surveillance. The median probability of survival in patients of the "study cases" was 7.3 years for the T1, 5.6 years for T2, 6.8 years for T3, and 1.5 years for the T4 categories.

Over the course of the disease, metastases were totally found in 18 of the 117 "study cases" (15.4 %). Three patients revealed only lymph node metastases. 15 patients came up with distant metastases via haematogenic tumour spread (12.8 %). In three of these patients, delayed lymphogenic metastases were also found. Distant metastases were most frequently present in the skeletal system, particularly in the spine and occasionally in other bones. The second most frequent location of metastases was the lung with five observed cases, four of which had additional osseous metastases. In 4 of 15 cases distant metastases were also detected in liver (Table 1).

Table 1 Distant/hematogen metastases in 15 of 117 study patients with sinonasal adenocarcinoma of intestinal Type (7 × autopsies)

Localisation	
Skeletal	14
Vertebra	10
Humerus	2
Rips	1
Skullcap	1
Pelvic	1
Lung	5
Liver	4
Cerebrum	2
Skin	2
Peritoneum	1
Medulla	1
Adrenal	1
Myocardium	1

Secondary neoplasias were confirmed in 18 of the 117 patients of the "study group" representing seven prostate carcinomas, four lung carcinomas, two oropharyngeal squamous cell carcinomas, and single case of each colon carcinoma, thyroid carcinoma, renal cell carcinoma, CUP with peritoneal carcinosis, glioblastoma and chronic lymphatic leukaemia.

The most frequent cause of death was aggressive local growth of the ITAC into the cranial base with infiltration of the cerebrum followed by multiple metastases at various locations. Older patients frequently died due to various comorbidities (Table 2).

Reference cases

During the review procedure, 252 of 330 "reference cases" between 2002 and 2013 were diagnosed histologically to represent ITAC (76.4 %). Only a limited number of these tumours could be grouped in accordance with the TNM criteria due to incomplete records. In 22 of the 330 cases, the records provided no information about the local spread of the primary tumour. Sixty-six tumours could be assigned to category T1 (20.1 %), 114 to T2 (34.8 %), 62 tumours to T3 (18.9 %) and 86 carcinomas to T4 (26.2 %). In five of the 252 ITAC cases (2.0 %), the records stated the presence of regional lymphogenic metastases which were, however, histologically confirmed only in one of these cases. In 10 patients (4.0 %), the records indicated distant haematogenic metastases at the time of first tumour diagnosis.

In 14 cases (5.6 %), the records contained no information on neck dissections. Without counting these cases 47 of 238 patients (19.8 % of cases with ITAC) underwent cervical lymph node dissection. The frequency of this operation tends to increase over the recent years (Table 3). According to the available histological data, regional metastases in left and right cervical lymph nodes were confirmed in merely one case. This case represents a histologically unusual carcinoma with predominant neuroendocrine differentiation and only abortive gland formation but strong immunohistochemical reactions for CDX2 and CK20. All specimens from neck dissections of the other 46 patients were histologically free of carcinomas.

Discussion

Lymph node metastases in CRAC are common and relevant for both, prognosis and therapy [10, 11]. Based on our results and those of others (Table 4), lymph node metastases in ITAC are far less frequent than in CRAC ranging from 0.3 to 12 %, (Table 4) although their histological picture is very similar. If we pool the data of the literature and our results into two groups, "up to 5 % metastasis rate" and "over 5 % metastases", there are 536 cases on the one hand and 354 on the other. We here demonstrate that assessment of the frequency and the prevalent mode of metastasis in ITAC are clearly dependent on the time of

Table 2 Cause of death for 81 patients with sinonasal adenocarcinoma of intestinal Type (ITAC)

ITAC related (52 patients)	*n*	ITAC unrelated (29 patients)	*n*
Local progress	31	Cardiac deaths	12
Distant metastases	15	Secondary malignancies (glioblastoma	6
Cerebral haemorrhage	2	Prostate, lung, pancreas, CUP)	
Cerebral abscess	2	Stroke	4
Cerebral cramp	1	Pneumonia	2
Operative complication	1	Multimorbidity	2
		Ileus	1
		Cirrhosis	1
		Pulmonary embolism	1

87 of 117 study patients (74 %) died within 5 years (6 cases without information, 7 autopsies, 74 clinical data)

Table 3 Sinonasal Adenocarcinoma of intestinal Type with Neck dissection

Year	Number of patients	Neck dissection (%)
2000	5	20.0
2001	8	12.5
2002	15	21.4
2003	20	23.5
2004	22	0
2005	18	6.3
2006	21	11.8
2007	20	5.3
2008	18	22.2
2009	29	31.0
2010	20	20.0
2011	17	29.4
2012	14	28.6
2013	25	32.0

disease progression with different results when data were collected at the time of primary diagnosis or towards the end of the disease (compare "reference cases" vs. "study cases"). This difference also pertains to the impact of neck dissections.

It seems likely that the low rate of regional or lymphatic metastasis of ITAC might be due at least in part to the particular anatomy of the inner nose and paranasal sinuses which are known to have only few lymphatic vessels [14, 15]. This hypothesis is supported by the fact that squamous cell carcinomas in the sinonasal region exhibit far less regional metastases than those of the oropharynx with a dense network of lymphatic ducts [16, 17]. In addition to the anatomical situation, differences in the biology of these histologically very similar adenocarcinomas, CRAC and ITAC may also explain the diverse metastatic behaviour. For instance, the absence of adenoma–carcinoma sequence in ITAC, and immunohistological [3] and molecular pathological differences pertaining to signalling pathways [18, 19] argue for distinct cellular functions of both tumour types.

From 117 ITAC "study cases", neck dissections were carried out in 18 patients (15.4 %). From 238 ITAC "reference cases" with information on the status of lymph nodes, cervical lymphadenectomy was performed on 47 patients (19.8 %). Regional lymph node metastasis was found in merely 5 of the 65 ITAC patients who had undergone lymphadenectomy (7.7 %). Disregarding the three node-positive cases at secondary lymphadenectomy, only 2 out of 62 cases with neck dissection (3.2 %) presented carcinoma-positive lymph nodes. With respect to the total group of 369 ITAC patients, only eight (2.2 %) exhibited metastases in lymph nodes.

There are only few papers investigating metastasis of ITAC and most of them demonstrate that the number of haematogenic metastases clearly exceeds the lymphogenic ones (Table 4). Only one publication disagrees with this assessment [6]. The prevalence of the haematogenic spread may well be the result of infiltration of the osseous cranium and the cranial base by carcinoma cells. The large numbers of sinusoid blood vessels present in this anatomical region possibly facilitate haematogenic metastasis. Distant metastases in bones occurred most frequently in the spine. The second most frequent location of metastasis was the lung, often with simultaneous osseous metastases (3 from five observed cases). In 4 of the 15 cases, carcinomas were found in liver (Table 1). Despite their very similar histology, ITAC produce far less distant metastases than

Table 4 Frequency of metastases by sinonasal adenocarcinoma of intestinal type (ITAC)

Metastases					
Studies	No. of patients	Regional/lymphogen		Distant/hematogen	
		n	%	*n*	%
Florange [12]	51	1	2.0	"Rare"	
Barnes [4]	17	2	11.8	4	23.5
Barnes [4] pooled data	196	–	8	–	12
Schroeder [6]	89	4	4.5	2	2.3
Franchi [5]	41	4	9.8	9	22.0
Llorente [13]	79	1	1.3	7	8.9
Franchi [3]	62	2	3.2	7	11.3
Present data 2014	117	7	6.0	15	12.8
Study cases	15 prim. Nec. diss.	1	6.6	–	–
	3 sek. Nec. dess	3	100.0	–	–
Refer. cases 2014	238	1	0.4	10	2.9
	47 Nec. diss	1	2.1	–	–

CRAC. Moreover, distant ITAC metastases usually arise only after many years of tumour progression and frequently in patients with a tumour relapse.

Histological differentiation between metastases from CRAC and ITAC poses a particular challenge. This is true for metastases in bone, and in lung and liver. Although the CK7 reaction provides a means for immunohistochemical differentiation in principle, it is not always reliable in every single case [3, 20]. Further diagnostic evidence can be obtained by molecular pathological tests, such as the absence of K-ras mutations that is more likely in ITAC than in CRAC [21, 22]. The EGFR receptor can also be helpful in the differentiation of both tumours [23]. Further distinction can also be achieved using the CGH method [24] and/or MALDI analysis [25]. It should be noted, however, that most of these methods are not sufficiently specific to ensure unequivocally the identity of both tumours in every individual case.

It is interesting to note that patients with ITAC should have a higher chance to also acquire CRAC [26, 27] but previous studies failed to demonstrate the increased risk of CRAC in ITAC patients [28]. In the 117 "study cases" presented here, only 1 patient was diagnosed for additional CRAC. In 252 ITAC "reference cases", CRAC was recorded in nine (3.6 %) and colon adenoma in 10 patients (4 %). These data for CRAC in our ITAC group are within the range of the overall prevalence of CRAC for men in Germany [29].

Taken together, our results indicate that (1) lymphogenic metastasis in ITAC can be predicted at the time of first diagnosis to occur in less than 5 %. Consequently, elective primary neck dissection is not indicated as part of the routine treatment. This would also apply to radiation treatment of the clinical n_0-neck. (2) At advanced stages of ITAC, a haematogenic metastasis is not uncommon. With the incidence of 15 % they are by far more frequent than lymphogenic metastases. Metastases predominantly arise in the skeletal system, particularly in the spine, and also in lung and liver. (3) Our results do not indicate an increased risk of CRAC in ITAC patients.

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