Symposium: Head and Neck

The effect of intraarterial high-dose cisplatin on lymph nodes in oral and oropharyngeal cancer

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Abstract

AIM OF STUDY: To assess the effect of strictly local treatment [intraarterial chemotherapy (iaCHT) with high-dose cisplatin and parallel neutralization] in the primary oral and oropharyngeal cancer (OOSCC) on the dependent cervical lymph nodes. **PATIENTS AND METHODS:** Seventeen consecutive patients with OOSCC and clinically positive necks underwent a prospective blinded comparison of two pre-surgical fluor18-deoxyglucose (FDG)-positron emission tomography (PET) examinations: baseline examination 1 week before and follow-up examination 3 weeks after iaCHT. Maximal standardized uptake (SUVmax) values of lymph nodes were measured and compared with each other and histopathology. **RESULTS:** The SUVmax value of the primary and all neck lymph nodes with uptake decreased significantly. Twelve/17 patients having metastases revealed significant decrease ($P = 0.03$), and benign lymph nodes showed non-significant decrease of the SUVmax. All neck lymph nodes with uptake and nodal metastases showed a significant reduction ($P = 0.004$) of standard uptake values (SUV). **CONCLUSION:** A regional effect of intraarterial cisplatin is proven. To date, it is not clear whether this is due to decreasing inflammatory reaction or a translymphatic anti-neoplastic effect.

Key words: Head and neck cancer, intraarterial chemotherapy, lymph nodes, oral cancer, positron emission tomography, regional chemotherapy

Introduction

In the early 90s of the last century, Robbins introduced intraarterial chemotherapy (iaCHT) with high-dose cisplatin and systemic antagonization with sodium thiosulfate in combination with radiation as an attempt to treat anatomically and functionally unresectable head and neck cancer patients.[1] This regime was effective and well tolerable due to reduced toxicity. Although iaCHT is a local treatment of the primary tumor, Robbins and co-workers early noticed good response of nodal disease in the neck. This effect was ascribed to the concomitant radiation to the neck, but an isolated effect of local chemotherapy on the nodal metastases could not be ruled out and was also discussed by Robbins.[2] However, there was a chance to demonstrate this only in a setting without radiation or other treatment of the neck.

Several centers used iaCHT in a neoadjuvant preoperative setting[3-7] to reduce tumor size and hopefully the risk of local recurrences. In each of these studies, the evaluation of remission concentrated on the local tumor. The possible effect of iaCHT on the dependent lymph nodes has not been reported yet. The preoperative setting without concomitant treatment, however, would offer the opportunity to examine the important question: Is there an effect of strictly selective local treatment on the cervical nodes? This could have a therapeutic value, e.g. for the eradication of micro-metastases.

Access this article online

Quick Response Code:

Website: www.indianjcancer.com

DOI: 10.4103/0019-509X.102918

Benazzo and co-workers administered three cycles of intraarterial carboplatin without systemic antagonization, and found a nodal response rate of 64% evaluated by computer tomography (CT) and/or magnetic resonance imaging (MRI).[3] However, they perfused the metastatic nodes selectively too and that response never has been controlled histopathologically.

Imaging modalities like ultrasound, CT, or MRI have quite uncertain criteria for the malignancy of neck lymph nodes, especially in case of borderline, and change in size is the only criterion for the assessment of an effect of iaCHT.

The best modality would be a functional evaluation of the nodes in question, providing objectively measurable values. At the author's Department of Oromaxillofacial Plastic Surgery, examination of oral and oropharyngeal cancer patients using fluoro18-deoxyglucose (FDG)-positron emission tomography (PET) for pre-treatment staging is routine, in cooperation with the Department of Nuclear Medicine. Therefore, the changes in uptake of FDG in the cervical nodes following iaCHT of the primary could be examined. However, no attempt could be made to examine the influence of iaCHT on tumor regression of lymph node metastases because histopathologic examination of lymph nodes before iaCHT would have sacrificed the nodes of interest. The overall behavior of the uptake in FDG-PET after iaCHT in head and neck cancer was already described in a paper by the authors.[8]

These prerequisites gave the opportunity to assess the effect of local chemotherapy in the oral cavity and the oropharynx on the lymph nodes of the neck.

Patients and Methods

In the period between July 2004 and August 2005, 17 consecutive patients suffering from previously untreated, histologically confirmed oral and oropharyngeal squamous cell carcinoma (OOSCC) were staged according to TNM[9] using locoregional inspection, palpation, ultrasound, CT, a chest X-ray, and "whole-body" FDG-PET. All showed pathological local and neck uptake in the baseline FDG-PET examination, and all showed suspicious neck findings in the CT examination, but without evident proof except in two patients with nodal (N) classification N2a, who displayed gross neck disease with central necroses.

After initial staging based on FDG-PET, all patients underwent neoadjuvant intraarterial chemotherapy with high-dose cisplatin (150 mg/m^2) with parallel systemic neutralization using sodium thiosulfate (9 g/ m^2), as demonstrated in the study of Kovács from 2004. [10] Perfusion was strictly selective to the primary, and no lymph nodes were perfused additionally. Three to four weeks later, remission of the primary was graded as: CR = complete remission, i.e. a complete disappearance of local tumor mass; PR = partial remission, a reduction of local tumor mass of more than 50%; and SD = stable disease, a reduction of less than 50% or identical tumor mass. Then, surgery took place comprising local tumor resection and modified radical neck dissection type III of the affected neck sides. One patient with progressive disease was in bad physical condition [Eastern Cooperative Oncology Group (ECOG) performance state grade 2][11] and suffering from multimorbidity so that surgical treatment was not possible. This patient had a palpable ipsilateral neck node which showed secure clinical and radiological signs of malignancy (fixation, central necrosis).

Time interval between baseline PET and iaCHT was less than 1 week, and the PET follow-up was about 3 weeks after iaCHT and less than 2 weeks before surgery.

PET scanning

The FDG-PET studies were done in all patients using a whole body scanner (ECAT EXACT 47, Siemens). After fasting for 12 h (blood glucose level < 150 mg/dl), a mean activity of 283 ± 54 MBq of F-18-FDG, body weight adjusted, was injected in a resting state. Images were reconstructed with an iterative reconstruction algorithm (slice thickness 3.4 mm, pixel size 4.37 mm).

Data analysis

In a prospective analysis, the transaxial, sagittal, and coronal PET images of all patients were reviewed by two experienced observers who were blinded to the findings of other anatomic imaging modalities and the clinical data including histological findings.

In all patients, the maximal standardized uptake value (SUVmax) of the primary and of the cervical lymph nodes was measured semiquantitatively using lean body mass index correction based on a return on investment (ROI) analysis.[12] In case of more than one suspicious node per patient, the node with the highest uptake was noted in combination with its neck level. The SUVmax before iaCHT was compared to the post-chemotherapy value and the histopathology which was obtained after removal of the primary tumor in combination with neck dissection. The measured node could be matched to histopathology using the noted level.

In patients with negative neck histopathology, the pre- and post-chemotherapy SUVmax values were defined as measurements of non-malignant lymph nodes. This

was done because regional uptake in FDG-PET was not regarded as a proof of malignancy, and consequently, pathological negativity not an effect of iaCHT.

Statistical analysis

SUVmax values of the primary and the lymph nodes and the nodal metastases, respectively, are presented as median (25th percentile, 75th percentile). Comparisons between the non-malignant and malignant lymph nodes were carried out by the non-parametric Wilcoxon–Whitney U-test, and the intra-individual comparison of SUVmax values of the primary and the lymph nodes was made by non-parametric Wilcoxon-matched pairs test.

Statistical significance was assumed at a value of $P < 0.05$. Statistical analysis was performed with BIAS (Copyright Epsilon 1989–2002).

Results

Demographic and tumor data as the results are summarized in Tables 1 and 2.

Firstly, the results for the primaries treated with iaCHT are given. The baseline SUVmax and the follow-up SUVmax values of the primary ranged from 1.1 to 11 and from 1.1 to 12, respectively [Table 2]. The SUVmax of the primary decreased after iaCHT significantly from a median (25th percentile/75th percentile) of 6.2 (3.4/7.8) to 3.7 (2.5/6.7) ($P = 0.04$). In 13 patients, the SUVmax of the primary decreased, in one patient the SUVmax did not change after iaCHT, and in 3 patients the SUVmax of the primary increased. These changes in metabolism show the local impact of iaCHT very well.

Table 2 also shows the clinical assessment of local response by inspection and palpation resulted in 11 complete (CR) and partial remissions (PR), and 6 patients with stable disease (SD). The primaries experienced histopathologic "down-staging" as compared to the clinical tumor (T) classification in seven patients and "up-staging" in two patients. Eight patients remained in the same T category. The clinical assessment, therefore, reflected the overall change in metabolism better than the histopathologic examination.

Secondly, the results for the neck lymph nodes are given. In the baseline PET, the SUVmax values of the cervical lymph nodes ranged from 1.8 to 10.5 and in the follow-up PET from 0.9 to 5.5. All neck lymph nodes with uptake showed a median standard uptake value (SUV) of 3.5 (2.4/5.2) at baseline, which significantly decreased to a post-chemotherapy value of 2.4 (1.4/4.4) ($P = 0.004$). This significant decrease in metabolism shows a regional effect of iaCHT.

Table 1: Demographic and tumor data of the 17 examined patients of the study

Male/female	8/9
Age (years)	
Mean	62.1
Range	49–85
ECOG* Performance State, number	
0	6
I	10
II	1
Localization of primary	
Floor of mouth, number	7
Oral tongue, number	3
Oropharynx, number	2
Cheek mucosa and retromolar trigone, number	2
Mandibular mucosa, number	1
Maxillary gingiva, number	2
Clinical stage, number	
I	0
II	0
III	7
IVA	10
Pathological stage, number	
0	1
I	1
II	3
III	2
IVA	10
Clinical T classification, number	
T1	1
T2	2
T3	7
T4	7
Pathological T classification, number	
T0	2
T1	3
T2	4
T3	0
T4	7
No specimen but clearly T4	1
Clinical N classification, number	
N1	9
N2a	2
N2b	3
N2c	3
Pathological N classification, number	
N0	5
N1	5
N2b	5
N2c	1
No specimen but N+	1

*ECOG = Eastern Cooperative Oncology Group

In 12 out of 17 patients, cervical lymph node metastases were detected histopathologically (11/17)

Table 2: Results of local and regional examination using clinical examination, FDG-PET, and histopathology

Pat.	Age (years)	Site of primary	cT	cN	Clinical remission	pT	Primary pre	Primary post	LN pre rc	LN post rc	pN	LN size (mm)
1	73	Maxillary gingiva	4	2b	SD	2	8.2	7.5	2.4	1.9	0	18
2	49	Lateral floor of mouth	2	1	PR	1	5.4	3.7	3.0	2.4	1	13
3	57	Base of tongue	3	2b	PR	4	3.1	2.6	1.9	2.2	2b	20
4	85	Maxillary gingiva	4	2a	PR	[4]	7.8	12.0	3.5	3.0	X	No specimen
5	78	Mandibular alveolar rim	4	2b	SD	4	7.8	6.7	3.6	2.2	2b	15
6	63	Lateral FOM	4	1	PR	4	6.6	5.6	3.9	0	1	3
7	70	Lateral oral tongue	2	1	SD	2	5.8	3.5	10.5	0	0	8
8	59	Anterior FOM	3	1	CR	0	6.2	2.7	1.8	0.9	0	20
9	54	Anterior FOM	3	1	PR	2	6.8	2.4	5.8	5.2	0	18
10	55	Lateral FOM	3	2c	PR	4	11.0	3.9	8.7	4.5	1	2
11	64	Soft palate	4	2c	SD	4	9.3	6.7	3.9	3.3	2b	17
12	56	Lateral FOM	3	1	PR	2	3.6	2.7	2.3	2.3	2b	20
13	51	Lateral oral tongue	3	1	CR	1	6.2	1.9	7.7	5.5	1	7
14	68	Cheek mucosa	3	1	PR	0	1.7	1.1	2.3	0	2b	25
15	55	Lateral FOM	4	2a	SD	4	7.8	8.8	4.6	4.3	1	30
16	59	Lateral oral tongue	1	1	CR	1	1.1	1.1	3.5	3.5	0	9
17	60	Retromolar trigone	4	2c	SD	4	3.1	5.1	3.5	5.4	2c	39

FOM = Floor of mouth, cT = Clinical T classification, cN = Clinical N classification, CR = Complete remission, PR = Partial remission, SD = Stable disease, pT = Pathological T classification, primary pre = Local PET measurement before iaCHT, primary post = Local PET measurement following iaCHT, LN = Lymph node, LN pre rc = Corrected lymph node PET measurement before iaCHT, LN post rc = Corrected lymph node PET measurement following iaCHT, pN = Pathological N classification, FDG-PET = Fluor18-deoxyglucose-positron emission tomography

or were clinically clearly positive (1/17) (71%). In the baseline PET, the cervical lymph node metastases presented SUVmax values between 1.9 and 8.7, and in the follow-up examination the SUVmax values of the cervical lymph node metastases ranged from 2.2 to 5.5. The cervical lymph node metastases showed a significant SUVmax decrease from 3.6 (2.5/4.4) in the pre-treatment examination to 2.7 (2.2/4.5) after iaCHT ($P = 0.03$). Only in two patients with lymph node metastases, the SUVmax of the nodes increased from 1.9 to 2.2 and from 3.5 to 5.4, respectively. In another patient, the SUVmax remained stable at a value of 2.3. The histopathologically measured size of the lymph node metastases ranged from 2 to 39 mm [Table 2].

The SUVmax of the non-malignant lymph nodes ranged from 2.4 to 10.5 in the baseline PET, and from 0.9 to 5.2 in the follow-up examination. These lymph nodes decreased in most cases (4/5), but the SUVmax changes did not reach significance ($P = 0.13$). In one patient with a non-malignant cervical lymph node, the SUVmax remained stable at 3.5. The size of the non-malignant nodes ranged from 8 to 20 mm.

The pre-treatment SUVmax of the lymph node metastases (median: 3.6, 25th percentile/75th percentile: 2.5/4.4) did not differ significantly from the SUVmax of the non-malignant lymph nodes (median: 3.5; 25th percentile/75th percentile: 2.1/8.2) ($P = 1.0$).

The difference in significance of post-treatment results for metastatic and non-malignant neck lymph nodes points to an anti-neoplastic effect of iaCHT in these nodes.

Discussion

To the best of our knowledge, there are no reports on the regional effect of strictly local iaCHT in oral and oropharyngeal cancer. Therefore, it is impossible to compare our results with those of other teams. This is due to the fact that iaCHT is commonly used in combination with radiotherapy.[1,2] The present investigation used FDG-PET, offering exactly measurable values to demonstrate a possible regional effect of local treatment. However, it cannot be stated whether this effect of iaCHT might be anti-neoplastic because an uptake in the neck cannot be interpreted as a proof for a lymph node metastasis. The findings in CT were also mainly ambiguous. An anti-neoplastic effect in lymph nodes would be very much desirable, and there are hints that this is the case.

A first evidence of such an anti-neoplastic effect was found during the analysis of sentinel node biopsy results. The rate of occult metastases in 366 patients with cN0 disease presented at The Second International Conference on

Sentinel Node Biopsy in Mucosal Head and Neck Cancer was 29% revealed by, and an additional 4% not revealed by sentinel node biopsy.[13] In our department, sentinel node biopsy has been carried out since 2000,[14,15] and the upstaging rate in patients treated with pre-surgical iaCHT with high-dose cisplatin revealed by scintigraphic lymph node mapping and sentinel node biopsy has been 12% due to sentinel nodes, and an additional 4% due to non-sentinel nodes. All patients without further neck treatment remained free of neck metastases to date (mean follow-up: 31.5 months).

This lower rate of occult metastases detected by sentinel node biopsy was suggested to be a result of an anti-neoplastic effect of iaCHT by Werner who speculated about an eradication of some of the micro-metastases which otherwise could have been found in the sentinel nodes without pre-surgical iaCHT.[16] However, the overall low rate of occult metastases might be a result of patient selection done by staging using PET, as the present author already discussed elsewhere.[17]

Nevertheless, it is proven that local chemotherapy has an impact on dependent lymph nodes via lymphatic drainage as could be demonstrated for breast cancer. Chen and colleagues treated breast cancer using lymphatic chemotherapy and found drug concentrations in the axillary lymph nodes.[18] It is absolutely imaginable that drugs administered locally using the arteries diffuse into the lymphatics and reach the lymph nodes, causing anti-neoplastic effects.

Squamous cell cancers of the oral cavity and the oropharynx are lesions of the mucosa in a region of regular bacterial colonization. This inevitably leads to superinfection with consecutive nodal reactions. In case of nodal metastasization, the proportion of additional inflammatory changes is very difficult to assess using any of the known imaging modalities. Consequently, it is difficult to distinguish between malignant and non-malignant neck lymph nodes, both harboring a certain amount of inflammation. Examinations comparing inflammation and malignancy using PET are known for other organs. For pancreatic carcinoma, investigators choose a threshold of 3.5 for the SUV in case of inflammatory changes and assessed values of about 6.4 as tumor.[19] Another working group found mean SUV values of 3.09 for pancreatic cancers and 0.87 for pancreatic inflammations,[20] and still another defined SUV values of 1.8 ± 4 for normal pancreatic tissue and found values between 3.1 and 5.4 for inflammatory changes; patients with pancreatic cancer had mean SUV values of 5.2 ± 2.2.[21]

It is generally known that limitations exist for PET with regard to false-positive results. Acute or chronic inflammation as well as unspecific reactions following radiotherapy may mimic tumor tissue.[22] A study in mice observed an increased FDG uptake in benign lymph nodes and peritumoral granulation tissue as a result of inflammatory reaction (activated macrophages).[23] In a case report, changes in fluorine-18-FDG uptake during radiotherapy were measured in a patient with two lymph node metastases of a papillary thyroid carcinoma. It was not possible to quantify the loss of tumor tissue and the parallel increase of inflammation in the nodes.[24] A study from our department several years ago comprising head and neck cancer patients showed a large range for the SUV of lymph node metastases (2–11) with a mean of 3.7 which did not differ much from the range of the SUV of benign lymph nodes (2–15.8).[25] It must be stated that to date, it is impossible to define a clear cut-off point of SUV, which discriminates between metastatic and non-malignant nodes.

Similarly, it cannot be stated whether the results presented in this study demonstrate a decreasing inflammatory reaction or an anti-neoplastic effect of cisplatin. To our knowledge, however, it is the first report of a nodal effect of local iaCHT with systemic neutralization without the possibility of any interaction of radiotherapy. The mechanism of cisplatin to arrive into the lymph nodes could be hematogenous or lymphatic. However, iaCHT with parallel neutralization results in very low blood levels of cisplatin,[26] so lymphatic drainage is likely. To prove an anti-neoplastic effect in the lymph nodes of human beings would be very difficult. An assessment of tissue platinum in the lymph nodes harbors a certain risk for diagnosis because half of the nodes must be sacrificed and cannot be examined for metastases.[18] Scanning electron microscope (SEM) examinations of the histological specimens could be a solution. Another possibility would be performance of pre-therapeutic ultrasound-guided fine needle aspiration of all suspicious lymph nodes in the neck. However, the present study shows that iaCHT is not likely to kill large metastases, and micro-metastases can be found in nodes which are not suspicious at all. Additionally, this method has the risk of either missing micro-metastases or eradicating them by the biopsy.

However, other research teams have found similar indications to lymphatic chemotherapy in sentinel nodes. Yokoyama and colleagues started from the mentioned discussions around sentinel nodes in head and neck cancer[13] and used iaCHT in five patients with tongue cancer. They found different cisplatin levels in sentinel and in non-sentinel nodes following neoadjuvant iaCHT, which led them to the suspicion of the possibility of a translymphatic spread of the drug.[27] Further studies are necessary.

Conclusion

The strictly local treatment (iaCHT) of primary oral and oropharyngeal cancers resulted in a significant decrease of metabolism in the dependent cervical lymph nodes which proves a distant effect of that treatment. It is very likely that this effect is translymphatic, but to demonstrate this, further studies are needed.

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How to cite this article: Kovács AF, Döbert N, Engels K. The effect of intraarterial high-dose cisplatin on lymph nodes in oral and oropharyngeal cancer. Indian J Cancer 2012;49:230-5.
Source of Support: Nil, **Conflict of Interest:** Nil.

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