

# Response evaluation after chemoradiotherapy for advanced staged oropharyngeal squamous cell carcinoma: a nationwide survey in the Netherlands

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Received: 11 October 2014 / Accepted: 2 November 2014 / Published online: 6 November 2014  
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**Abstract** Following failure of chemoradiotherapy (CRT) for advanced staged oropharyngeal squamous cell carcinomas (OPSCC), residual tumor can often be treated successfully with salvage surgery, if detected early. Current clinical practice in the VU University Medical Center is to perform routine response evaluation, i.e., examination under general anesthesia (EUA), 12 weeks after treatment. However, in the Netherlands there is no consensus on response evaluation in patients with advanced oropharyngeal cancer. Questionnaire on current clinical practice concerning response evaluation after CRT for advanced OPSCC in all eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group. The response rate was 100 %. Response evaluation was routinely performed with various methods in five institutions (62.5 %) and in one institute (12.5 %) only if clinical evaluation was difficult. Two centers (25 %) did not perform response evaluation. In case of suspicion of residual disease during follow-up, six centers (75 %) performed imaging prior to EUA and two centers (25 %) only if clinical evaluation was difficult. Diagnostic techniques used prior to EUA were MRI (87.5 %), diffusion-weighted MRI (37.5 %), 18F-FDG-PET-CT (75–87.5 %) and CT (37.5 %). This survey shows a substantial variation in the diagnostic policy concerning response evaluation after CRT for advanced OPSCC in the Netherlands. There is a

need for guidelines for response evaluation in patients with advanced oropharyngeal cancer.

**Keywords** Oropharyngeal cancer · Chemoradiotherapy · Response evaluation · 18F-FDG-PET-CT · DW-MRI · Examination under general anesthesia

## Introduction

Head and neck cancer is the sixth most common cancer worldwide [1] and in the Netherlands, each year 270 new patients with oropharyngeal squamous cell carcinoma (OPSCC) are diagnosed. Advanced stage disease accounts for 80 % of all oropharyngeal carcinomas [2]. Formerly, irresectable OPSCC was treated by radiotherapy with or without chemotherapy and patients with resectable OPSCC were treated with a combination of surgery and radiotherapy. Surgery often led to functional and cosmetic morbidity, leading to a diminished quality of life. Nowadays, resectable OPSCC is also treated with chemoradiotherapy (CRT) with the intention to preserve organ function and to maintain quality of life, resulting in acceptable locoregional control rates [3–5].

After failure of CRT, residual tumor of initially resectable OPSCC can be treated successfully with salvage surgery, if detected timely. In case of late detection and delayed salvage surgery, local control and survival rates rapidly decrease [6]. However, salvage surgery is associated with considerable risks [7] and will only be performed after histopathological confirmation of viable tumor cells. Therefore, current clinical practice in the VU University Medical Center is to routinely perform response evaluation, i.e., examination under general anesthesia (EUA), 12 weeks after the end of treatment, to detect residual

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disease as soon as possible. However, the incidence of residual disease after CRT is low. In this manner, many patients are exposed to unnecessary biopsies in treated areas, inducing pain, inflammation and wound healing problems [8]. Besides, due to sampling errors within the residual mass, biopsies in previously irradiated areas may be false negative [6]. Moreover, an EUA requires hospital stay and operating facilities. Current clinical practice to try and identify patients who may benefit from salvage surgery needs to be improved. This requires a diagnostic strategy which accurately selects patients who should undergo invasive EUA, without compromising the benefit of timely detection of residual disease.

Functional imaging techniques such as 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG-PET-CT) and diffusion-weighted magnetic resonance imaging (DW-MRI) may be useful in this setting [9]. PET-CT combines imaging of metabolically active tissues with anatomical information. Due to increased glycolytic activity, higher concentrations of 18F-FDG accumulate in malignant tumors than in normal tissue [10]. DW-MRI characterizes tissue based on the differences in water mobility, which is related to cellularity [11]. Post-treatment nontumoral tissue changes are expected to show less cellularity than viable tumor tissue [12]. However, at present, there are no national guidelines for the diagnostic policy concerning response evaluation after CRT for advanced OPSCC.

The aim of this study was to evaluate the current clinical practice. A questionnaire was sent to head and neck surgeons (as representatives) in the eight head and neck cancer centres of the Dutch Head and Neck Oncology Cooperative Group (Nederlandse Werkgroep Hoofd-Halstumoren).

## Materials and methods

In 2014, a questionnaire on current clinical practice concerning response evaluation after CRT for advanced OPSCC was sent to clinicians in all eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group. The questionnaire (Table 1) was accompanied by an explanatory letter.

## Results

All questionnaires were returned completed. In seven institutions (87.5 %), both the head and neck surgeon (otolaryngologist or maxillofacial surgeon) and the radiotherapist performed the clinical follow-up in OPSCC patients after CRT. In one of these centers (12.5 %), the medical oncologist was also standard involved in the

clinical follow-up. In one center (12.5 %) only the radiotherapist performed the clinical follow-up. In these patients, response evaluation was performed with a variety of methods in five institutions (62.5 %); four centers performed response evaluation in all patients and one center performed response evaluation only in patients with an initially resectable tumor. One center (12.5 %) performed response evaluation if clinical evaluation was difficult and two centers (25 %) did not perform response evaluation at all. Response evaluation, if implemented, was performed varying from 8 to 12 weeks after end of CRT, but most centers (5 out of 6) performed response evaluation 12 weeks after the end of CRT. The techniques which are routinely used for response evaluation, are shown by institution in Table 2a.

Besides performing imaging for response evaluation, in three centers (37.5 %), routine imaging after CRT was also performed to establish a new baseline situation for future comparisons, in patients with suspected residual disease during follow-up. Four centers (50 %) did not perform routine imaging after CRT and one (12.5 %) performed imaging after CRT to establish the new situation if clinical evaluation was difficult. The methods used for establishing the new situation are shown in Table 2b.

In case of clinical suspicion of residual disease during follow-up, six centers (75 %) performed imaging prior to EUA and two centers (25 %) only performed imaging prior to EUA in case clinical evaluation was difficult or in case no definable tumor was manifest. Table 2c shows the different diagnostic imaging techniques that were used in case of suspected residual disease. A large variation is reported by the institutes which techniques and in what combination these techniques are used for response evaluation, establishing the new anatomy or detection of residual disease: CT, MRI, 18F-FDG-PET-CT, ultrasound [with fine needle aspiration cytology (FNAC)], chest CT and EUA.

If 18F-FDG-PET-CT was performed, seven centers (87.5 %) applied dedicated high-resolution protocols for the head and neck area (instead of whole body imaging). One center (12.5 %) just performed whole body PET-CT imaging. Two centers sometimes used beta-blockers (such as propranolol) to reduce the uptake in brown fat in a research protocol or if the nuclear medicine physician considers it useful. Another center reported the use of benzodiazepines to avoid unwanted uptake in neck musculature. Five centers (62.5 %) reported standard quantitative Standardized Uptake Values ( $SUV_{mean}$  and/or  $SUV_{max}$ ) and in one center (12.5 %) SUV-values were determined on request. In the other two centers (25 %), SUV-values were not determined for clinical purposes.

If MRI was performed after CRT, this included DW-MRI in five centers (62.5 %). However, only three centers (37.5 %) based clinical decisions on the result of the DW-

**Table 1** Questionnaire on current practice concerning response evaluation after CRT for advanced OPSCC

Q.1	Who performs the follow-up in patients treated with CRT for OPSCC? ( <i>more than 1 answer allowed</i> ) (a) Otolaryngologist/ head and neck surgeon (b) Radiotherapist (c) Medical oncologist
Q.2	Do you routinely perform response evaluation in these patients? (a) Yes, always (b) Yes, but only in patients with an initially resectable tumor (c) Sometimes, please explain: ..... (d) No, only in case of suspicion of residual disease/ complaints ( <i>move to question 5</i> )
Q.3	Which technique(s) do you use for response evaluation? ( <i>more than 1 answer allowed</i> ) (a) Physical examination (b) CT (c) MRI (d) Ultrasound (with FNAC) (e) 18F-FDG-PET-CT (f) EUA (g) Other, i.e.: .....
Q. 4	When do you perform response evaluation? ( <i>open question</i> )
Q. 5	Do you routinely perform imaging in patients with OPSCC after CRT to establish the new situation (which can be of value later on, in patients with suspected residual disease during follow-up)? (a) Yes, always (b) Yes, but only in patients with an initially resectable tumor (c) Sometimes, please explain: ..... (d) No ( <i>move to question 8</i> )
Q. 6	Which imaging technique(s) do you use to establish to new situation? ( <i>more than 1 answer allowed</i> ) (a) CT (b) MRI (c) Ultrasound (with FNAC) (d) 18F-FDG-PET-CT (e) Other, i.e.: .....
Q. 7	When do you perform these imaging techniques of the new situation? ( <i>open question</i> )
Q. 8	Do you perform imaging before EUA in case of suspicion of residual disease? (a) Yes (b) Sometimes, please explain: ..... (c) No ( <i>go to question 10</i> )
Q. 9	Which imaging technique(s) do you use in case of suspicion of residual disease? ( <i>more than 1 answer allowed</i> ) (a) CT (b) MRI (c) Ultrasound (with FNAC) (d) 18F-FDG-PET-CT (e) Other, i.e.: .....
Q. 10a	Is diffusion-weighted imaging performed during MRI? (a) Yes (b) No ( <i>move to question 11</i> )
Q. 10b	Do you take the results of DW-MRI into consideration? (a) Yes (b) No
Q. 10c	Which b-values are used to perform DW-MRI? ( <i>open question</i> )
Q. 10d	Are quantitative ADC-values determined? (a) Yes (b) No
Q. 11a	Are dedicated head and neck images made during 18F-FDG-PET-CT? (a) Yes (b) No, just a whole body PET-CT
Q. 11b	The PET-CT is made after .... minutes post injection of 18F-FDG ( <i>open question</i> )
Q. 11c	Is a beta-blocker used to reduce the uptake in brown adipose tissue? (a) Yes (b) No
Q. 11d	Is a benzodiazepine used to avoid unwanted uptake in muscles? (a) Yes (b) No
Q. 11e	Are quantitative SUV-values determined? (a) Yes (b) No ( <i>go to question 12</i> )
Q. 11f	Which SUV-values are determined? ( <i>more than 1 answer allowed</i> ) (a) $SUV_{mean}$ (b) $SUV_{max}$ (c) Other, i.e.: .....
Q. 12	Do you standard take a biopsy during the EUA? (a) Yes (b) No, only in case of clinical suspicion
Q. 13	Do you look at the results of the imaging prior to the EUA? I.e. is your decision to perform a biopsy based on imaging? (a) Yes (b) No, my decision to perform a biopsy is not based on imaging (c) No, I did not perform imaging prior to EUA

ADC apparent diffusion coefficient, CT computed tomography, CRT chemoradiotherapy, DW-MRI diffusion-weighted magnetic resonance imaging, EUA examination under general anesthesia, FNAC fine needle aspiration cytology, OPSCC oropharyngeal squamous cell carcinoma, PET-C positron emission tomography, SUV standardized uptake value

**Table 2** Techniques routinely used by institution for (A) response evaluation, (B) establishing the new situation after therapy to facilitate follow-up and (C) in case of suspected of residual disease

Centers	A. Response evaluation	B. Establishing new situation	C. Suspicion residual disease
1	MRI, ultrasound (with FNAC) <sup>a</sup>	None	MRI, PET-CT, ultrasound (with FNAC) <sup>b</sup>
2	CT or MRI, ultrasound (with FNAC) <sup>a</sup>	CT or MRI, ultrasound (with FNAC) <sup>a</sup>	CT or MRI, PET-CT <sup>d</sup> , ultrasound (with FNAC) <sup>a</sup>
3	None	None	CT, MRI, PET-CT, ultrasound (with FNAC) <sup>a</sup>
4	MRI, ultrasound (with FNAC) <sup>a</sup>	MRI <sup>a</sup>	MRI, PET-CT <sup>a</sup>
5	None	None	PET-CT <sup>b</sup>
6	CT, MRI <sup>a</sup>	None	CT, MRI, chest CT <sup>c</sup>
7	MRI, PET-CT <sup>b</sup>	MRI <sup>b</sup>	MRI, PET-CT <sup>a</sup>
8	MRI, PET-CT, EUA <sup>c</sup>	MRI, PET-CT <sup>c</sup>	MRI, PET-CT, ultrasound (with FNAC) <sup>a</sup>

CT computed tomography, MRI magnetic resonance imaging, EUA examination under general anesthesia, FNAC fine needle aspiration cytology, PET-CT positron emission tomography-computed tomography

<sup>a</sup> In every patient

<sup>b</sup> Only if clinical evaluation is difficult

<sup>c</sup> Only in patients with an initially resectable tumor

<sup>d</sup> In case of planned salvage surgery

MRI. In the other two centers, DW-MRI had recently become available and the scan protocol was still under development. In the three centers with DW-MRI experience, different b-values and number of b-values were used. All centers used the b-values 0 and 1000, two centers added b750 or b800 to the MRI protocol. At the time of the questionnaire, three centers (37.5 %) did not have experience with DW-MRI.

In seven centers (87.5 %), the head and neck surgeons looked into the results of the imaging techniques, if available, prior to the EUA to determine the location of a eventual biopsy. All head and neck surgeons only took a biopsy in case of clinical suspicion of residual disease during EUA.

## Discussion

It is of great importance that CRT can be implemented without compromising locoregional disease control. Early detection in case of residual tumor is an important prognostic factor, since survival rates decline with delayed salvage surgery [6]. In this survey we found a large variation among the institutes which examinations and in what combination these examinations were used for response evaluation. Most institutes offensively pursue potential residues, probably leading to a high rate of futile diagnostic procedures due to the fairly good response rates after CRT. Alternatively, other institutes perform careful clinical observation throughout the course of treatment and during follow-up without performing diagnostic procedures with potential morbidity and costs. However, this harbors the risk of delaying the diagnosis of residual tumor and

potentially reduces the chances for surgical cure and survival [6, 13]. There is a need for national guidelines for response evaluation in patients with advanced oropharyngeal cancer.

The yield of EUA in the detection of residual OPSCC after CRT may be improved by patient selection based on imaging techniques. Based on a series of 46 patients with OPSCC treated with radiotherapy, Ojiri et al. showed a high negative predictive value for CT. CT findings with grade 0 (no focal lesion and no asymmetry) and grade 1 (anatomic asymmetry or discrete mass <10 mm) always suggested good control at the primary site [14]. Van den Broek et al. applied these Ojiri criteria to MRI in 82 patients with mostly oral and oropharyngeal cancer who were treated with CRT. The authors concluded that one can refrain from EUA in patients with MRI findings grade 0 or 1 [15]. However, these conventional anatomy-based investigations have limitations and can be difficult to interpret, since post-treatment changes including fibrosis, oedema and necrosis obscure accurate assessment [16]. In a retrospective study at our institute, the interpretation of MR imaging performed 3 months after chemoradiation showed only ‘moderate’ interobserver variability [17] between two radiologists (Cohen’s Kappa,  $\kappa = 0.52$ ) for the primary tumor in 86 patients [manuscript in preparation].

Potential methods to improve the distinction between residual tumor and aspecific post-radiation tissue are functional imaging with 18F-FDG-PET-CT and DW-MRI [9]. For 18F-FDG-PET performed with a mean of 38 days after treatment, Kitagawa et al. [18] showed a sensitivity of 100 % and a specificity of 89.5 % in a prospective study with 23 oral cancer patients treated with CRT (with an incidence of residual disease of

17 %). Based on a series of 92 HNSCC patients treated with (chemo)radiation, Moeller et al. [19] found a sensitivity of 70 % and a specificity of 94 % for 18F-FDG-PET-CT conducted 8 weeks after the end of treatment. In another prospective study, Krabbe et al. [20] demonstrated in 48 patients with oral or oropharyngeal cancer treated with curative intent (surgery, radiotherapy or a combination), that 73 % of the futile EUAs could be avoided with 8 % of the local residues missed when 18F-FDG-PET-CT was performed 3 months after treatment. To summarize, 18F-FDG-PET(-CT) can be used as an additional tool in response evaluation to select patients who should undergo EUA without a high risk of missing residual disease. However, there is a lack of clear response criteria for test positivity. The guideline for standardization of 18F-FDG-PET-CT by Boellaard et al. [21] enables the comparison of study results, since the examinations should be consistent between institutes that acquire the data. Optimization of response criteria should be addressed in larger multicenter studies.

PET-CT imaging is usually conducted as whole body imaging, with a relatively low resolution. Hence, for PET-CT imaging of a complex anatomic region like the head and neck area, whole body imaging is less appropriate. Moreover, the CT part is performed as a low-dose non-contrast CT, which is adequate for anatomic correlation of the PET images and attenuation correction, but only a high-dose CT scan with contrast offers diagnostic image quality. A few studies recommend dedicated high-resolution protocols for the head and neck area, especially for the detection of small lymph node metastases [22, 23]. The present survey demonstrates the use of dedicated head and neck PET-CT protocols in 87.5 % of the head and neck cancer centers in the Netherlands.

In 18F-FDG-PET-CT imaging, unwanted physiological uptake of 18F-FDG may occur in the neck musculature and vocal folds not only due to movement or talking, but also due to uncomfortable waiting conditions [24, 25]. Benzodiazepines, which have muscle relaxant activity, can be used prior to administration of 18F-FDG to avoid unwanted uptake. Using the protocol for the standardization of multicenter PET studies by Boellaard et al. [25], muscle uptake can be minimized by means of patient instructions and optimal resting conditions.

Another source of false positive results is caused by tracer uptake in areas of brown adipose tissue (BAT). BAT is often closely related to important lymph node groups in the neck and supraclavicular region. Its metabolism is influenced through activation of  $\beta$ -adrenergic receptors. Administering  $\beta$ -adrenergic antagonists (e.g., propranolol) prior to 18F-FDG injection can reduce tracer uptake in BAT and can lead to improved assessment of PET-CT imaging [26, 27]. Currently, only two centers in the

Netherlands sometimes use propranolol in head and neck oncology patients.

DW-MRI can also be used to monitor treatment response. King et al. [28] showed that DW-MRI with Apparent Diffusion Coefficients (ADC) performed 6 weeks after (chemo)radiation was an early marker for locoregional failure in a post-treatment mass. Vandecaveye et al. [29] reported significantly lower  $\Delta$ ADC in lesions with later tumor recurrence than in lesions with complete remission, in a study with 29 HNSCC patients and DW-MRI performed 3 weeks after CRT. DW-MRI is also increasingly used for the detection of recurrent HNSCC after treatment, in patients with a clinically suspected recurrence. In a pilot study with 30 patients, Abdel Razek et al. [30] showed that DW-MRI provided promising results for discriminating recurrent tumors from postoperative or postradiation changes. Tshering Vogel et al. [31] included 46 patients for MR imaging with a median of 14 months after (chemo)radiotherapy and achieved good diagnostic accuracy. Vandecaveye et al. [32] concluded in a study with 26 patients that DW-MRI can differentiate between persistent or recurrent HNSCC and nontumoral tissue changes after CRT. Taken together, DW-MRI might have additional value to differentiate between residual or recurrent tumor and post-treatment changes. DW-MRI is non-invasive and takes only a few minutes extra for patients who already undergo an MRI. However, only a few studies with small patient groups have been performed. These results need to be validated in larger studies. In addition, a wide variation in ADC values of recurrent tumor and postradiation effects have been reported. The use of different scan protocols (e.g., DWI sequence, b-values, field strength) can explain this variation. Future research should address developing uniform DWI protocols.

The optimal timing of post-treatment 18F-FDG-PET-CT and DW-MRI imaging is a subject of debate. Response evaluation in the Netherlands is performed varying from 8 to 12 weeks after end of CRT, but 82.5 % of the centers perform response evaluation 12 weeks after CRT. 18F-FDG-PET-CT performed prior to 10 weeks after the end of CRT is related to high rates of false negative results, perhaps because residual viable tumor cells did not have adequate time to repopulate to a level that can be detected by PET-CT [33, 34]. False positive findings also occur due to inflammation and post-radiation soft tissue effects, particularly present early after CRT [34]. Early detection of residual disease is important to allow for prompt salvage treatment when the size of residual tumor is still limited. DW-MRI seems to have prognostic value in this early post-treatment phase, as previous described results from the literature suggest [28, 29]. There is currently no consensus for optimal timing of post-treatment imaging in head and neck cancer patients.

In conclusion, this survey shows a substantial variation in the diagnostic policy concerning response evaluation after CRT for advanced OPSCC between the eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group. There is a need for guidelines for response evaluation in patients with advanced oropharyngeal cancer. Functional imaging, such as 18F-FDG-PET-CT and DW-MRI, may be helpful in diagnosing residual disease and avoiding futile EUA. Further multi-center prospective studies and optimization of response criteria are warranted.

**Acknowledgments** The authors would like to thank prof. dr. M.W.M. van den Brekel, drs. A. Navran, dr. R.P. Takes, dr. G.B. Halmos, dr. L.A. van der Velden, drs. F. Smit, drs. W.W. Braunius, dr. C.A. Meeuwis, dr. K.W. Kross for completing and returning the questionnaire, as representatives of their respective head and neck cancer centers.

**Conflict of interest** The authors declare that they have no conflict of interest.

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