Response assessment after induction chemotherapy for head and neck squamous cell carcinoma: from physical examination to modern imaging techniques and beyond

Remco de Bree, MD, PhD,[1] **Gregory T. Wolf**, MD,[2] **Bart de Keizer**, MD, PhD,[3] **Iain J. Nixon**, MBChB, PhD,[4] **Dana M. Hartl**, MD, PhD,[5,6] **Arlene A. Forastiere**, MD,[7] **Missak Haigentz Jr.**, MD,[8] **Alessandra Rinaldo**, MD, FRCSEd *ad hominem*, FRCS (Eng, Ir) *ad eundem*, FRCSGlasg,[9] **Juan P. Rodrigo**, MD, PhD,[10,11] **Nabil F. Saba**, MD,[12] **Carlos Suárez**, MD, PhD,[11,13] **Jan B. Vermorken**, MD, PhD,[14] **Alfio Ferlito**, MD, DLO, DPath, FRCSEd *ad hominem*, FRCS (Eng, Glasg, Ir) *ad eundem*, FDSRCS *ad eundem*, FHKCORL, FRCPath, FASCP, IFCAP[15]

[1]Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Department of Otolaryngology-Head and Neck Surgery, University of Michigan Health System, Ann Arbor, MI, USA
[3]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
[4]ENT Department, NHS Lothian, Edinburgh, UK
[5]Department of Otolaryngology-Head and Neck Surgery, Institut Gustave Roussy, Villejuif Cedex, France
[6]Laboratoire de Phonétique et de Phonologie, Sorbonne Nouvelle, Paris, France
[7]Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[8]Department of Medicine, Division of Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA
[9]University of Udine School of Medicine, Udine, Italy
[10]Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain
[11]Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
[12]Department of Hematology and Medical Oncology, The Winship Cancer Institute of Emory University, Atlanta, GA, USA
[13]Fundación de Investigación e Innovación Biosanitaria del Principado de Asturias, Oviedo, Spain
[14]Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium
[15]Coordinator of the International Head and Neck Scientific Group

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Corresponding author:
Remco de Bree, MD, PhD
Department of Head and Neck Surgical Oncology
UMC Utrecht Cancer Center
University Medical Center Utrecht
Heidelberglaan 100, 3584 CX Utrecht
P.O. Box 85500, 3508 GA Utrecht
The Netherlands
e-mail: r.debree@umcutrecht.nl

Abstract

Significant correlations between the response to induction chemotherapy and success of subsequent radiotherapy have been reported and suggest that the response to induction chemotherapy is able to predict a response to radiotherapy. Therefore, induction chemotherapy may be used to tailor the treatment plan to the individual head and neck cancer patient: following the planned subsequent (chemo)radiation schedule, planning a radiation dose boost or reassessing the modality of treatment, e.g. upfront surgery. Findings from reported trials suggest room for improvement in clinical response assessment after induction chemotherapy, but an optimal method has yet to be identified. Historically, indices of treatment efficacy in solid tumors have been based solely on systematic assessment of tumor size. However, functional imaging, e.g. FDG-PET potentially provides an earlier indication of response to treatment than conventional imaging techniques. More advanced imaging techniques are still in an exploratory phase and not ready for use in clinical practice.

Key words: head and neck squamous cell carcinoma; induction chemotherapy; response assessment; FDG-PET

Introduction

The achievement of complete tumor regressions after systemic chemotherapy has been a hallmark of progress in the medical management of solid malignancies. Prior to the early 1970's, the role of chemotherapy for patients with head and neck cancer was largely limited to palliation of incurable disease. The observations of frequent and significant tumor regressions after chemotherapy alone in previously untreated patients led to the introduction of chemotherapy prior to surgery or radiation in potentially curable patients in expectation of tumor responses that might permit a reduction in conventional treatment modalities and provide the rationale for subsequent use of chemotherapy as an adjuvant after treatment.[1] Small studies of chemotherapy alone for laryngeal cancer have reported high rates of complete and durable responses, but the evidence level for chemotherapy alone is low.[2,3] Thus, the early development of chemotherapy regimens for head and neck cancer uniquely focused on the use of systemic chemotherapy as induction treatment prior to local treatment modalities. Since that time, the use of induction chemotherapy in the management of locally advanced head and neck squamous cell carcinoma (HNSCC) has grown. Understanding the effects of induction chemotherapy on the biology of the tumor prior to delivery of definitive treatment (i.e. (chemo)radiation or surgery) is paramount to provide as much information as possible in order to tailor the treatment plan to the individual patient: following the planned subsequent (chemo)radiation schedule, planning a radiation dose boost or reassessing the modality of treatment.

Induction chemotherapy, also known as neoadjuvant chemotherapy, has been investigated as a strategy to shrink or downstage locoregionally advanced head and neck cancers, increase organ preservation rates and/or reduce the risk of locoregional and/or distant recurrences.[4] The largest meta-analysis (MACH-NC) studying the effect of chemotherapy - adjuvant, neoadjuvant or concomitant- on overall and event-free survival included 87 trials and 16485 patients. Induction chemotherapy reduced the risk of distant metastases with a hazard ratio of 0.73.[5] A more recent meta-analysis of 14 trials and 2099 patients found no significant difference in overall survival, disease free survival, or locoregional recurrence between previously untreated patients with resectable non-metastatic HNSCC patients treated with induction chemotherapy followed by locoregional treatment (surgery and/or radiotherapy with or without concomitant chemotherapy) compared to those with locoregional treatment only.[6] This discrepancy is difficult to explain, but may possibly be due to a difference in primary

tumor sites and stages between these different meta-analyses.[7] Significant correlations between the response to induction chemotherapy and success of subsequent radiotherapy have been reported and suggest that the response to induction chemotherapy is able to predict a response to radiotherapy.[8-12] It has been consistently demonstrated in nearly every trial of induction chemotherapy that the survival of responding patients is superior to that of non-responding patients, suggesting that chemotherapy response is one of the strongest and most reliable prognostic indicators.

The differing clinical responses to induction chemotherapy could lead to different outcomes of (chemo)radiotherapy, with good response leading to high rates of locoregional control by non-surgical treatment and poor response leading to low rates of locoregional control. Therefore, induction chemotherapy may be used to select patients with resectable HNSCC for organ preservation by (chemo)radiotherapy. It has been well-recognized that in patients with laryngeal and hypopharyngeal cancer who respond to induction chemotherapy, followed by (chemo)radiotherapy, instead of radical surgery, organ preservation can be achieved, without a negative impact on overall or disease-free survival.[6,9] For other head and neck tumor sites there is no conclusive evidence that induction chemotherapy offers the benefit of organ preservation.[6] Using induction chemotherapy for deintensification of radiation therapy, particularly in HPV-associated oropharyngeal carcinoma, is currently being investigated.[13]

In order to assess response to induction chemotherapy without the need for pathological assessment of resected surgical specimen, there is great interest in surrogate metrics for histopathological response. In other tumors, e.g. osteosarcoma, locally-advanced breast cancer and esophageal cancers, which are treated by neoadjuvant chemotherapy and/or radiotherapy followed by radical surgery, histopathological examination of the surgical specimen reveals the histologic response to the neoadjuvant treatment. However, if surgical resection is not planned, alternative methods of assessment are needed.
Historically, indices of treatment efficacy in solid tumors have been based solely on systematic assessment of tumor size. Changes in tumor size, particularly complete clinical regression after treatment and the speed of tumor response are often, but not invariably, related to treatment outcome.[14]

In contemporary practice, conventional contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) provide the mainstay of imaging for treatment response

assessment. Both rely on tumor morphology to evaluate disease, whereas functional imaging such as positron emission tomography (PET) and diffusion weighted (DW) MRI provide complementary information about the underlying tumor biology such as metabolic activity and cellularity. Changes in tumor metabolism tend to occur early in course of therapy and therefore precede reduction in tumor size.

Therefore, functional imaging potentially provides an earlier indication of response to treatment than conventional imaging techniques. This not only can act as a prognostic indicator but in addition may allow for adaptation of definitive treatment planning at a time when this is still feasible. In particular, changes in 18-fluorodeoxyglucose (FDG) uptake (determined by standardized uptake values: SUV) and microscopic water motion (determined by apparent diffusion coefficient: ADC) are potentially useful for assessment of treatment response. Other techniques include dynamic contrast-enhanced and perfusion CT and MRI. Optimal timing and interpretation criteria for use of functional imaging in daily practice have yet to be developed.

A variety of approaches for measuring response rate have been developed including the World Health Organization (WHO) criteria (1979),[15] Response Evaluation Criteria in Solid Tumors (RECIST) (2000)[16], RECIST 1.1 (2009)[17], European Organization for Research and Treatment of Cancer (EORTC) criteria for PET (1999)[18], National Cancer Institute (NCI) guidelines (2006)[19] and PET Response Criteria in Solid Tumors (PERCIST) (2009)[20]. Because of variability in measurements and techniques, clinically useful absolute change values reflecting tumor response are lacking. These various classifications divide intrinsically continuous data into bins, losing statistical power in favour of ease of nomenclature and convenience in clinical practice.

Rapid assessment of treatment effect may allow clinicians to shift patients away from ineffective to effective therapies at an earlier stage (response-adaptive or risk-adaptive treatment). Such an approach is an attractive possibility in the drive towards personalized care. Early assessment of therapeutic efficacy is a key issue in considering the potential benefit of upfront surgery or of treatment escalation (e.g. radiation dose boost) in a non-responder or avoidance of the unnecessary toxicity and costs of ineffective treatments. It is important to realize that a complete metabolic response following induction chemotherapy does not always represent sufficient log cell kill to translate into durable local control, and cure is then achieved by subsequent definitive therapy. That said, the frequent observation of

pathological complete responses with chemotherapy alone in HNSCC has been exploited experimentally in small numbers of very highly selected patients demonstrating potential for long-term disease-free survival.[21]

Response assessment in randomized clinical trials

Randomized clinical trials (RCT) are considered by many to be the most reliable form of scientific evidence in the hierarchy of evidence that influences healthcare policy and practice. This is because RCTs help to reduce spurious causality and bias. Results of RCTs may be combined into systematic reviews and meta-analyses which are increasingly used in the pursuit of evidence based medicine. Recently, a meta-analysis on induction chemotherapy in patients with resectable HNSCC was performed by Ma et al .[6] From this meta-analysis all full papers were selected for review of the response assessment of induction chemotherapy. Response criteria, technique (physical examination and/or imaging) and effect of response assessment are summarized in Table 1[1,10,22-36]. In the majority of studies, response to induction chemotherapy was assessed by clinical examination, sometimes combined with CT. However, the utilization of endoscopy for objective tumor evaluation has not been fully validated.[16,37] The majority of studies used WHO criteria for response assessment. Unfortunately, in most studies, details of clinical assessment for tumor regression were not specified.

Some studies show that there is room for improvement in response assessment in categories which currently include complete regression, partial regression, stable disease and progressive disease. In a study of the Southwest Oncology Group (SWOG) the rate of clinical complete response (definition and diagnostic techniques not reported) was 19% whereas the rate of pathological complete response (after induction chemotherapy all patients underwent surgery) was 13%, suggesting that the clinical assessment used at that time (1980-1985) was not able to detect all residual disease.[23]

In the final report of the Head and Neck Contracts Program[22] in which a single cycle of cisplatin and bleomycin induction chemotherapy was used, a false positive rate for histologic complete response was 82%; of the 22 patients with clinical complete response, 18 had still microscopic tumor evident in the surgical specimen. In contrast, 6 of 114 (5%) patients with clinical partial responses had no evidence of cancer in the resected primary tumor.[22] The EORTC study (1978-1984) in 97 oral and oropharyngeal cancer patients also noted a discrepancy between clinical and histopathological regression after induction chemotherapy.

Of the 6 patients with clinical complete regression, only 4 patients had pathological complete regression. Of the 46 patients with 50% or more clinical regression only 31 (67%) patients had a pathological regression (defined as disappearance of living tumor cells (CR) or persistence of islets of living tumor cells (PR)). Finally, of 48 patients with clinical regression of less than 50%, 3 (6%) were found to have a pathological complete regression.[25]

Maipang et al[28] reported that in 3 of the 9 (33%) patients with clinical or radiological complete response after two courses of induction chemotherapy, tumor was still detected histologically.[28] In the Veterans Affairs study (started in 1985) on advanced laryngeal cancer, a difference in clinical and pathological assessment results were found; pathologically confirmed complete regression was found in 88% of the patients with clinical complete response and 45% of those with partial response.[8]

In a study by Zhong et al[38] 222 patients with advanced stage oral squamous cell carcinoma were randomized between induction chemotherapy (2 cycles of docetaxel, cisplatin and 5-fluorouracil) followed by radical surgery and postoperative radiotherapy (54 to 66 Gy) versus up-front radical surgery and postoperative radiotherapy. Of 124 patients who received induction chemotherapy, 8.1% were considered to have had a clinical complete response but 13.4% achieved a pathologic complete response. Clinical tumor response was determined by clinical evaluation and imaging studies (performed at baseline and 2 weeks after cycle two of induction chemotherapy). The imaging studies were not further specified. Responses were characterized according to RECIST criteria.[38]

The reported findings suggest room for improvement in response assessment after induction chemotherapy, but an optimal method has yet to be identified.

Morphological response assessment

Imaging at baseline and after 1 or 2 cycles of (induction) chemotherapy can be performed to estimate whether the treatment is effective in that specific tumor and patient. Contrast-enhanced CT and MRI provide the mainstay of imaging for response assessment in head and neck cancer. The proposed methods to assess treatment response by WHO criteria include determining the bi-dimensional measurements of tumors, whereas for RECIST/RECIST1.1 only uni-dimensional measurements are used.[16,17] According to WHO criteria, for a clinically complete response no tumor is visible and for a partial response, tumor is visible but a reduction of more than 50% of the product of two perpendicular diameters is observed, which is confirmed after an interval of at least 4 weeks.[15] The major reference for justifying a 50%

decrease as a criterion for tumor response was based on an experiment in which experienced oncologists had to assess solid wooden spheres placed on a soft mattress and covered with a layer of rubber foam by palpation. Because of measurement errors, the assessed sizes of identical spheres differed by at least 25% in 25% of the measurements and by at least 50% in only 6.8% of measurements, which was considered acceptable. Thus, if a reduction of 25% in the product of the perpendicular diameters of the 'tumors' was considered a response, an unacceptable high false tumor reduction occurred 25% of the time. However, when a 50% threshold was applied the error fell to an acceptable 7% false positive rate.[39,40]

RECIST criteria, developed by NCI and EORTC, define response as a 30% decrease in the largest diameter of the tumor. For a spherical lesion, this measure is equivalent to a 50% decrease in the product of 2 diameters (as used in WHO criteria). Using RECIST, changes (for at least 4 weeks) are categorized as complete response, partial response, stable disease or progressive disease. Measurable lesions (used for assessment of response) are defined based on longest diameters, because in smaller lesions the risk of changes by chance is higher. A good concordance was found between response assessment using RECIST and WHO criteria for the four bins of response in the same patients recruited in 14 different trials. The most precise estimates are achieved when the same imaging technique is used and the same reader assesses the baseline and follow-up evaluations; more misclassifications and variance in response are noted with different readers. Tumor size is clearly an important parameter.[16] Due to the irregular 3-dimensional shapes of many head and neck tumors, particularly for the oral cavity, the maxilla and the larynx, RECIST criteria may not be sensitive for predicting response after chemotherapy, as found by Patil et al in a small study showing a low correlation between RECIST response and response on pathological examination.[41]

Traditionally, the morphologic response to therapy has been performed with two-dimensional measurements of size. Advances in CT and MRI technique and software technology have led to considerable refinements in the accuracy of tumor size measurements facilitating tumor volume measurements. Baghi et al[42] found a significant difference in tumor volume before and after three cycles of induction chemotherapy (docetaxel, cisplatin and 5-fluorouracil) in 50 HNSCC patients.[42] In 78 patients with laryngeal cancer treated with definitive radiation, Issa et al[43] found that CT estimated pretreatment tumor volumes (both primary tumor and composite volumes including nodes) were highly prognostic of success, but that this prognostic value was absent after a single cycle of induction chemotherapy, suggesting that tumor volume assessment after induction chemotherapy is not of prognostic significance .[43]

However, further research on value of volume measurements for clinical response evaluation are warranted. For clinical trials morphological measurements according to RECIST 1.1 are recommended (Table 3).[17]

Morphologic measurements are most often used, but have limited value in response assessment after induction chemotherapy to individualize further treatment.

Functional response assessment

Conventional CT and MRI rely on morphology to evaluate disease. In contrast, functional imaging such as PET, diffusion weighted (DW) and dynamic contrast-enhanced (DCE) MRI and other advanced functional imaging techniques provide complementary information on the underlying biology. This information includes metabolic activity, cellularity, vascularity and oxygenation, all of which are potential mediators of chemotherapy and radiation resistance. The reduction in metabolic signal as depicted on functional imaging can significantly exceed reductions in morphological volume as defined on CT or MRI.[44] A minimum of 10 days delay between a chemotherapy cycle and FDG-PET scanning permits bypassing of the chemotherapeutic effect and transient fluctuations of FDG-PET that may occur early after treatment (stunting or flare of tumor uptake). This 'metabolic flare' is a transient increase in FDG uptake and is thought to consist of two effects: an increased metabolism due to cellular stress and an influx of FDG due to damaged cellular membranes.[45]

In several small studies, early therapeutic response on FDG-PET and DW-MRI after two cycles of induction chemotherapy in patients with advanced stage HNSCC seems to be a predictive factor for recurrence free survival after subsequent chemoradiation.[46]

FDG-PET

Although a range of factors have been associated with 18F-FDG uptake, there appears to be a rather strong relationship between FDG uptake and cancer cell number. Therefore, it is reasonable to expect that decreases in tumor FDG uptake would be seen with a loss of viable cancer cells.

Although a completely negative PET scan at the end of therapy typically suggests a good prognosis, it does not necessarily correspond to a complete absence of cancer cells, as FDG-PET is unable to discriminate between minimal tumor burden and no tumor burden. Because FDG uptake is usually not absent in patients who respond well to treatment, prognostic stratification between high and low FDG uptake after or during treatment using absolute cut-

off values or cut-off thresholds for percentage decline have been advocated. Metabolic activity and changes due to treatment can be assessed in various ways: qualitative or quantitative; binary (yes or no response), classified (several groups) or continuous (giving varying degrees of response); in the most metabolic active region or the entire tumor volume; in only the primary tumor, the maximal number of lesions or all lesions; from the same lesion or the most intense lesion (not necessarily the same as the most intense lesion on the other scan).

For early (subtle) changes in tumor uptake before the ultimate treatment effect is complete, quantification may be more desirable than qualitative scoring. Response does likely represent a continuum of intensities of uptake. Because PET is intrinsically a quantitative imaging method, quantitative measurement of early treatment-induced changes is an attractive tool for measuring subclinical response and more complete changes. More than 30 different ways to assess tumor response by PET quantitatively have been reported, but standardized uptake values (SUV) are the most widely applied, generally correlating well with more complex analytic approaches. SUV is a widely used metric for assessing tissue accumulation of tracers. SUV can be normalized to total body mass, lean body mass or body surface area. While these SUV normalization approaches will give different absolute change in SUV with effective treatment and different absolute amount of change to be significant different from a previous scan, the percentage changes with treatment will be comparable in a single patient with a stable weight and identical patient preparation and scan protocol.[20]

A wide variety of region of interest (ROI) selection metrics has been used: manually defined ROI (tumor delineation), isocontour ROIs based on a fixed percentage of the maximal pixel in tumor, fixed SUV threshold, or a background-level threshold and fixed dimension. The most frequently used SUV metric is the SUV obtained from the pixel with the highest uptake within the tumor (SUVmax). Another SUV metric is SUVpeak, which is defined as the average SUV within a small, fixed-size region of interest (a 1 cm^3 volume spheric ROI) centered on a high-uptake part of the tumor [20]

SUV reproducibility, which is important in clinical practice, is mainly dependent on ROI and lesion size. Small lesions may have low uptake of FDG due to partial volume effect. SUVmax can easily be measured using modern commercial workstations and is most resistant to partial volume effect in small tumors, but is highly dependent on the pixel size. SUVpeak in a small volume of greatest metabolic activity in the tumor is less subject to variance than is a small, single pixel SUVmax. Since SUVs of small lesions are more susceptible to measurement

faults, tumor sizes should be noted and should be 2 cm or larger in diameter for accurate measurement, though smaller lesions of sufficient FGD uptake, including those not well seen anatomically, can be assessed. Generally, lesions must be clearly visible and both large enough and hot enough to evaluate changes in SUV.[20] Standardization, as proposed in the United States[19] and Europe[36], is essential to achieve reproducible SUVs.

A variety of methods has been used to determine the change in SUV associated with treatment. Absolute SUV and percentage decline in SUV can both be used to assess treatment response. The ratio of SUV is less dependent on ROI choice than absolute SUV determinations and is therefore preferred.[47] Moreover, using absolute SUV decline in multicenter studies and comparing between reported studies may be difficult due to inadequate standardization of SUV determination. An SUV decline of 30-35% is usually associated with a good outcome. However, the decline warranted for achievement of treatment goal may be dependent on tumor type, treatment performed and time interval following treatment.[47]

In patients with multiple lesions, several strategies to assess response to therapy by SUV decline have been described: 1) assessment of SUVmax (the single, most intense area in the primary tumor (not necessarily the same area), which is considered to coincide with the worst-case biologic behaviour of malignancy) decline of the primary tumor only, because changes in SUV of the primary tumor seem to predict the outcomes in metastases quite accurately; 2) the smallest percentage decline in SUVpeak of a lesion as representative, with the rationale that the lesion with the worst response would determine survival. [20]

The medically relevant cut-off value for a SUV decline to optimally represent response and predict outcome may differ on the basis of disease, the timing after treatment, the treatment itself and the treatment goal. Early during treatment, lower cut-off values may be used than following completion of treatment. Also, for induction chemotherapy this cut-off value may be lower as further treatment is foreseen. This cut-off value can be used for response-adaptive treatment, e.g. (concurrent) (chemo)radiotherapy with eventual additional cycles of induction chemotherapy for responders or surgery with or without postoperative radiotherapy in non-responders. Decisions to deny probably ineffective therapy depend on alternative therapeutic options available and on the risk, costs and perceived benefits of available treatment options. In the case of false positive findings, when induction chemotherapy is followed by

radiotherapy instead of defaulting to surgical resection, tumor relapse is more likely to occur. This may then require salvage surgery with a higher risk of postoperative complications. With regard to predicting further response to subsequent radiotherapy, it is not always essential to achieve histopathological complete response after induction chemotherapy.

The delay in translating PET as response metric from research to clinical practice is probably due to the variability in study performance (imaging protocol) and the lack of uniformly practiced response metrics for PET. Standardized approaches to the performance of PET and to machine calibrations have been articulated.[19,47] Qualitative and quantitative approaches for PET treatment response assessment have been postulated.[16,20]

In the response evaluation criteria in solid tumours (RECIST) 1.1 FDG-PET scanning may only be incorporated to complement CT scanning in assessment of progression.[17] The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. Recently O et al[48] report on a simplified guide to PET response criteria in solid tumors (PERCIST) 1.0, which describes in detail methods for controlling the quality of FDG-PET imaging conditions to ensure the comparability of PET images from different time points to allow quantitative expression of changes in PET measurements for an assessment of overall treatment response in PET studies. PERCIST uses the peak SUV corrected for lean body mass (SULpeak) and defines criteria for measurable lesions. In short, responses are categorized in: 1) complete metabolic response: complete resolution of FDG uptake; 2) partial metabolic response: a decrease of greater than or equal to 30% and of at least 0.8 SUL units between the most intense evaluable lesion at baseline and follow-up (not necessarily the same lesion); 3) stable disease: an increase or decrease in SULpeak of less than 30%; 4) progressive disease: an increase greater than or equal to 30% and an increase of at least 0.8 SUL units in target lesion or development of a new lesion (Table 4).[20,48] For functional response assessment using FDG-PET in clinical trials PERCIST criteria are recommended.

Clinical studies

Dalsaso et al[49] performed CT and FDG-PET prior to and after 2 or 3 cycles of paclitaxel and carboplatin in 19 patients with advanced head and neck cancer. A suboptimal reference standard was used: four biopsies from 4 separate sites within the tattooed primary tumor area

before treatment. A significant difference in mean reduction of SUVmean was found in complete pathologic responders, defined as patients with negative biopsies after chemotherapy (82%) as compared to patients having residual disease (35%). Although no significant difference in mean reduction in tumor volume by CT between these patient groups was observed, a significant correlation between percent reduction of SUVmean and percentage reduction in CT tumor volume following chemotherapy was found.[49]

In locally advanced HNSCC patients, Brun et al[50] found that patients who had an SUVpeak of FDG lower than the median value after one cycle of chemotherapy or 12-40 Gy radiotherapy have a higher tumor response and better survival as compared to those with a higher than median SUVpeak. Unfortunately, patients who underwent FDG-PET after induction chemotherapy were not separately evaluated.[50]

McCollum et al[51] analyzed the FDG-PET results of 26 patients with advanced stage head and neck cancer after 3 cycles of induction chemotherapy with cisplatin and 5-fuorouracil with or without docetaxel. When the outcome of histopathological examination of a biopsy from the primary tumor site was used as reference standard, a high sensitivity (100%) and negative predictive value (100%) but a low specificity (65%) and positive predictive value (27%) were found for detecting persistent disease at the primary site. However, the possibility of false-negative results from biopsy specimen sampling errors could not be ruled out.[51]

FDG-PET and CT were compared with endoscopy and biopsy under general anesthesia 3 weeks after a single course of induction chemotherapy with cisplatin or carboplatin and 5-fuorouracil in 12 patients with resectable advanced stage oropharyngeal cancer by Chepeha et al.[37] During endoscopy under general anesthesia after induction chemotherapy, the percent of residual primary tumor was estimated by the surgeons relative to the tattoo markings made during the pretreatment endoscopy. Endoscopy was used as reference standard and to decide whether to continue with non-surgical treatment (concomitant chemoradiation followed by adjuvant chemotherapy if response at least 50%) or subsequent surgery with postoperative radiotherapy (if response lower than 50%). Although SUVmax values were determined for each tumor, these SUV values were only used as addition to visual estimation of response and not for calculation of SUVmax change. Tumor volumes were assessed on CT. The agreement between PET and endoscopy was substantial and the agreement between CT and endoscopy fair. They suggest that FDG-PET is more reliable than CT for predicting tumor response, although the reference standard was not ideal. The authors hypothesize that FDG-PET can replace endoscopy with biopsies for assessment of tumor response after induction chemotherapy.[37]

Argiris et al [52] reported on a series of 39 patients with locally advanced head and neck cancer who underwent induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab. Response assessment was performed after 3 cycles of this induction protocol by CT, physical examination and FDG-PET portion of PET/CT. Complete response by PET was defined as complete disappearance of FDG activity attributable to malignancy, without regard to the degree of CT response, as assessed on combined PET–CT. Substantial differences in complete response rate as assessed by CT, physical examination and PET were reported: for primary tumor 48%, 70% and 58% and for lymph node metastases 5%, 34% and 21%, respectively.[52]

Kichuchi et al[53] evaluated the predictive value of sequential FDG-PET/CT after one cycle of neoadjuvant chemotherapy (the platinum complex CDGP and the oral fluoropyrimidine derivate S-1) in 16 HNSCC patients. They used the SUVmax of 15 primary tumors and 11 (largest) lymph nodes and grading of histopathological regression as the reference standard (response: less than 10% vital tumor in tumor bed; non-response 10% or more vital tumor in tumor bed). Although two different PET/CT scanners were used, sequential PET/CT scans before and after induction chemotherapy were performed using the same protocol and scanner for each patient. Post-chemotherapy SUVmax (cut-off point 3.5) and percentage decline in SUVmax (cut-off point 55.5%) were shown to predict histopathological responses with a sensitivity of 71% and 86%, a specificity of 89% and 95%, a positive predictive value of 71% and 86% and a negative predictive value of 89% and 95%, respectively. MRI findings based on longest diameter before and after chemotherapy were not to predict histopathological response in these same patients.[53] In a later study Kichuchi et al[54] used the same SUVmax decrease threshold of 55.5% for defining responders and non-responders to induction chemotherapy by FDG-PET/CT evaluation in comparison to RECIST with MRI evaluation. Only non-responders revealed by FDG-PET/CT were significantly linked to poor local tumor control rate and disease specific survival (hazard ratio 4.9).[54]

Yoon et al[55] evaluated the efficacy of FDG-PET after two cycles of induction chemotherapy (S-1 and cisplatin) in 21 advanced stage head and neck cancer patients who achieved partial response to predict clinical outcome after concurrent chemoradiation. Patients who attained a complete response (according to RECIST) after concurrent chemoradiation showed a significantly higher decrease in SUVmax compared to patients who failed to attain a complete response. A SUVmax of at least 4.8 on FDG-PET after induction chemotherapy and a decrease from baseline of at least 65% in SUVmax after induction chemotherapy predicted

complete response after concurrent chemoradiation and progression free and overall survival.[55]

The potential of FDG-PET/CT after two (or three) cycles of docetaxel, cisplatin and 5-fluorouracil to predict disease-free survival in 15 patients with locally advanced HNSCC treated by induction chemotherapy preceding concomitant chemoradiation was evaluated by Abgral et al.[46] Metabolic response was assessed by the measurement criteria of the EORTC. The 1-year disease-free survival of metabolic responders, defined as at least 25% decrease (between baseline and after two cycles induction chemotherapy) of SUVmax, was statistically significantly better than non-responders (100% vs. 20%, p=0.0014).[46]

A greater reduction in FDG-avid volume and hence metabolic signal than in reduction of volume on conventional imaging (CT and MRI) following induction chemotherapy was observed by Powell et al.[44]

FDG volumetric imaging parameters to assess response to induction chemotherapy were used by Yu et al[56] in 28 advanced stage HNSCC patients who underwent 3 cycles of TPF chemotherapy (docetaxel, cisplatin and 5-fluorouracil) followed by chemoradiation. Different parameters for metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were evaluated. A reduction of 42% of MTV and 55% of TLG were predictive of progression free survival after subsequent chemoradiation with a sensitivity of 67% and 63% and a specificity of 90% and 90%, respectively.[56]

In a preliminary study, Gavid et al[57] assessed the correlation between reduction in SUVmax and in metabolic tumor volume (measured from isocontours of SUV=2.5) following a first cycle of induction TPF chemotherapy (docetaxel, cisplatin and 5-fluorouracil) and clinical response as assessed by endoscopy with taking of biopsies after 2 or 3 cycles induction chemotherapy in 21 advanced stage HNSCC patients. Using this suboptimal reference standard, advanced stage HNSCC patients with ≥ 70% tumor reduction on endoscopy and negative biopsies were considered to be responders and continued with chemoradiation, whereas non-responders underwent surgery. Responders showed a significantly greater mean SUVmax reduction between PET-CT examinations pre-treatment and after 1 cycle of chemotherapy. Responders tended to show greater reduction in hypermetabolic volume than non-responders.[57]

Semrau et al[57] performed response assessment using FDG-PET/CT and endoscopic evaluation after a single cycle of induction chemotherapy using docetaxel and cisplatin or carboplatin in 47 patients with advanced stage HNSCC. Responders achieving a ≥ 30% decrease in endoscopic tumor size and a ≥ 20% decrease in SUVmax proceeded to chemoradiation and

non-responders to surgery. In 89% of these patients metabolic and clinical response were similar. Using this strategy of selecting patients for chemoradiation or surgery a local control rate of 86% was obtained.[58]

Assessment by PET-CT and DW-MRI after the first cycle of induction chemotherapy (docetaxel, cisplatin and 5-fluorouracil) in 20 patients with advanced stage HNSCC who received 2 cycles of induction chemotherapy followed by concomitant chemoradiation was reported by Wong et al[59]. Responders, defined as patients without persistent disease at response assessment at 3 months following completion of chemoradiation with MRI, PET-CT and clinical examination, showed a significantly greater reduction in metabolic tumor volume and total glycolysis both measured for ROI with uptake of $\geq$ 40% of SUVmax and with SUV $\geq$ 3.5.[59]

Recently a systematic review on the effectiveness of FDG-PET/CT for evaluating early response to induction chemotherapy in HNSCC was performed. Seven studies including a total of 207 patients with advanced stage HNSCC were included. The authors concluded that a meta-analysis was not possible because the selected studies were heterogeneous concerning response criteria, reference standards, chemotherapy strategy and endpoints. However, six from seven studies concluded that FDG-PET allowed early evaluation response to induction chemotherapy and predicted survival outcomes.[60]

The studies cited above demonstrate the potential of FDG-PET to assess response to induction chemotherapy in order to select patients for treatment adaptation, i.e., concomitant chemoradiation or surgery. Unfortunately different parameters have been used for response assessment. Moreover, SUV cut-offs identified in (single center) studies involving a specific set of patients may not be applicable to other centers with different equipment, patient populations, chemotherapy regimens and clinical imaging protocols. Reporting the SUV changes as figures and not only as PERCIST criteria would be helpful to assess the most useful cut-off value, as otherwise the advantages of the continuous output of PET data are lost through forced categorization.

If induction chemotherapy is used to select patients with resectable HNSCC for organ preservation by (chemo)radiotherapy, response assessment would preferably performed after only one cycle in order to avoid further unnecessary treatment with its associated burden, toxicity and morbidity. In Table 2 studies using FDG-PET for response assessment after induction chemotherapy are ordered according timing of assessment. Unfortunately due to

aforementioned heterogeneity only the conclusion can be made that even after one cycle FDG-PET is very promising for this purpose.

More recent advances in imaging

Diffusion-weighted MRI

Diffusion-weighted (DW-)MRI which provides maps of microscopic water motion within biologic tissues, offers a simplistic approach (as compared to CT perfusion and DCE-MRI) to physiologic changes within the tumor after treatment. Higher cellularity (e.g. malignant tumor) is generally associated with more restricted diffusion (lower apparent diffusion coefficient (ADC) values).

Because ADC measurements are dependent on a high number of adjustments which differ between scanners and protocols, results from studies are not generally applicable across different institutes, hampering its implementation.[61] Changes in ADC values are probably less dependent on DW-MRI scanners and protocols than absolute ADC values.

Cytotoxic therapy triggers tumor cell death, leading to reduced density with a subsequent increase in ADC after treatment. Berrak et al[62] evaluated the potential of DW-MRI in monitoring the treatment response of the largest metastatic cervical lymph node in patients with HNSCC undergoing cisplatin based induction chemotherapy. Each patient underwent MRI on the same of the two scanners used. Changes in nodal volume, signal intensity on T2 and ADC were not different for complete and partial responders at different clinical endpoints. Although no difference in changes in nodal volume and signal intensity on T2 were found between survivors and those who died from HNSCC, a significant difference in percentage change in ADC between those patient groups was observed.[62] In the previously mentioned study of Wong et al[59] a trend was observed for a higher ADC on DW-MRI after one cycle of induction chemotherapy in responders compared to non-responders of induction chemotherapy followed by concomitant chemoradiation.[59]

Conventional DWI-MRI cannot separate perfusion and true diffusion-related effect. Intra-voxel incoherent motion (IVIM) imaging is characterized by 3 parameters: pure diffusion coefficient, microvascular volume fraction and perfusion-related incoherent microcirculation. IVIM-derived parameters may characterize the actual status of diffusion in tumors more accurately then conventional DWI because it provides both perfusion and true diffusion-related measurements. In a recent study by Guo et al[63] IVIM measurements were performed

before and after 2 cycles of paclitaxel and cisplatin induction chemotherapy in 28 patients with advanced stage hypopharyngeal carcinoma. Response was classified according to RECIST 3 weeks after the second cycle of induction chemotherapy by conventional MRI. The post-treatment ADC and pure diffusion coefficient were significantly higher in responders than in non-responders, whereas perfusion-related incoherent microcirculation was significantly lower in responders and microvascular volume fraction was not significantly different. Changes (between pre-treatment and 3 weeks after induction chemotherapy) of ADC, pure diffusion coefficient and perfusion-related incoherent microcirculation were significantly higher in responders, but microvascular volume fraction was not.[63]
DWI-MRI is a promising technique for response assessment, but further research using a standardized protocol is needed for eventual implementation in clinical practice.

CT and MRI perfusion

A number of methods have been developed for the measurements of tissue perfusion using CT and MRI. These methods can generally be grouped under 2 classes: compartmental analysis and deconvolution-based methods. Perfusion studies are obtained by monitoring a standard iodinated contrast of gadolinium bolus through a vascular bed.

Deconvolution-based CT perfusion is a fast imaging technique which can assess physiologic parameters such as blood flow (BF), blood volume (BV), mean transit time (MTT) and capillary permeability surface area product (CP) and provides data that can be useful in the detection and characterization of tumor. Significant perfusion differences of BF, BV, MTT and CP have been found in untreated HNSCC compared with adjacent normal tissue.[64] CT perfusion has been proposed as a new, possibly superior evaluation of tumor response. After intravenous injection of a bolus iodinated contrast agent, tissue and vessel attenuation changes can be observed during the first pass of the agent by dynamic image acquisition at a given anatomic level. Time-density curves can be constructed for observer-defined regions of interest (ROIs). Within limits of assumptions, tissue perfusion can be estimated based on observed density changes. The time course of the iodine concentration is a measure of the regional perfusion, and this concentration is linearly correlated to tissue density, as seen on CT. Several algorithms can be used to measure perfusion with CT. Gandhi et al[65] examined whether these CT perfusion parameters correlate with response to induction chemotherapy as assessed by endoscopy under general anaesthesia. In 9 advanced head and neck cancer patients, reduction in BV by more than 20% on CT perfusion 3 weeks after one cycle of

induction chemotherapy (cisplatin and 5-fluorouracil) showed substantial agreement with clinical response (≥50% reduction in tumor volume) as assessed with endoscopy. The agreement between decreased (≥20%) BF, decreased (≥20%) CP and increased (≥20%) MTT and clinical response was fair. Based on these results, the authors hypothesized that CT perfusion parameters could potentially replace invasive diagnostic procedures under general anaesthesia as a predictor of tumor response.[65]

Petralia et al[65] found a correlation between a decrease in both blood flow (BF) and blood volume (BV) on perfusion CT and tumor volume reduction in 20 patients with advanced stage head and neck cancer after 2 cycles of cisplatin and 5-fluorouracil as induction chemotherapy.[66]

In dynamic contrast enhanced (DCE-)MRI several parameters can be computed pixel-wise: transfer constant (K^{trans}), the volume of extravascular extracellular space per unit volume of tissue (Ve), the initial (60s) area under the gadolinium curve (IAUGC60) and the enhancing fraction (EF). Powell et al[44] reported a significant fall of the transfer constant Ktrans and IAUGC60 following chemotherapy.[44]

These advanced perfusion imaging techniques for response assessment are still in an exploratory phase and not ready for use in clinical practice.

Future development of response assessment

The clinical utility of imaging after induction chemotherapy but prior to subsequent locoregional therapy is based on the ability to predict clinical response and survival after sequential definitive therapy, i.e. concurrent (chemo)radiation or surgery. It is not always essential to achieve complete response after induction chemotherapy, because subsequent definitive (chemo)radiation may eradicate residual disease. Rough classification systems for tumor response have been used for decades because precise techniques were not or later not yet widely available. However, more recent morphological and functional imaging techniques may allow for more reliable reporting on changes during or after treatment. Therefore, individual figures can be used in reporting response assessment and categories can be made based on optimal cut-off values. Because new treatment paradigms and new imaging

modalities and techniques require continued re-evaluation of response assessment tools, recently the RECIST working group proposed organ specific modifications. However, these are not yet defined for head and neck cancer.[67]

Whereas WHO and RECIST criteria are historically focussed on a reliable assessment of any response after induction chemotherapy, new quantitative functional imaging techniques will determine a cut-off value for optimal prediction of response after subsequent chemoradiation. These cut-off values will be dependent on alternative treatment options, available treatment modifications and the opinion of patients and their clinicians. However, when new techniques are evaluated for their potential role in determination of response to induction chemotherapy, an initial correlation between imaging parameters and response have to be investigated.

Several studies suggest that functional imaging techniques show potential in determining response to induction chemotherapy when compared to morphological radiological or clinical assessments. However, the wide variety of methodologies and endpoints reported limit the conclusions which can be drawn at this stage. Nevertheless, functional imaging holds promise for more personalized treatment using induction chemotherapy to select HNSCC patients for definitive therapy.

Use of biomarkers for response assessment

A major goal of response assessment to induction chemotherapy is proper selection of patients for subsequent management based on the biologic response of the tumor to initial cytotoxic chemotherapy in anticipation of improved survival and/or organ preservation. However, if surrogate biomarkers could predict the response to chemotherapy, treatment selection for definitive therapy could be improved, toxicities reduced, redundant treatment avoided and perhaps other biologic methods to monitor response could be developed that would guide changes in therapy. [68,69] In general, it appears consistent that tumor or molecular characteristics that reflect rapid tumor growth or high cellular proliferation tend to correlate with responses to induction chemotherapy, while lack of aggressive growth, proliferation or invasiveness tend to predict better responses to surgical excision.

Response assessment after induction immunotherapy

Although the focus of this review is response assessment after induction chemotherapy, the immunotherapy of head and neck cancer is the most rapidly developing frontier of treatment and has been stimulated by the approval of several immune checkpoint inhibitors for clinical

use in patients with advanced cancers.[70,71] Further, induction immune modulation is gaining increasing popularity as a means to assess the clinical and immunologic effectiveness of these agents.[72] Like the development of induction chemotherapy approaches, methods to predict and appropriately assess tumor and immunologic responses after induction immune modulation are needed. It is unclear however, if the clinical or radiologic measures that have been proven useful after induction chemotherapy will be equally useful after immunotherapy since effects of immune mediated cytotoxicity tend to evolve more slowly than direct cytotoxic agents and may be accompanied by initial tumor swelling, acute inflammation or increased functional activity due to influx of tumor infiltrating lymphocytes. Appropriate metabolic imaging will likely be more meaningful than anatomic imaging. Considerable effort is underway to define both molecular and immune markers that predict success of immune modulation with the checkpoint inhibitors. Clearly what has been learned regarding the monitoring of tumor response to induction chemotherapy could have important implications for the development of induction immunotherapy regimens for patients with head and neck cancer. Patients with head and neck cancers will continue to represent an ideal model for future development of induction chemotherapy and immune therapy regimens and associated biomarkers to guide selection of appropriate definitive treatment modalities for more personalized care.

Conclusion

Induction chemotherapy may be used to tailor the treatment plan to the individual head and neck cancer patient: following the planned subsequent (chemo)radiation schedule, planning a radiation dose boost or reassessing the modality of treatment, i.e. upfront surgery. For this purpose reliable response assessment is needed. Response assessment after induction chemotherapy is currently probably most valuable if a choice between an organ-preservation approach (radiotherapy with or without chemotherapy) and surgery has to be made, particularly for hypopharyngeal and laryngeal cancer. Response assessment using conventional clinical morphological techniques is limited. Functional imaging, in particular using FDG-PET, is promising, but the introduction in routine clinical practice is limited due to the variability in study performance (imaging protocol) and the lack of uniformly practiced response metrics for PET. Research on other functional imaging techniques for response assessment is scarce and these techniques are still in an exploratory phase. Surrogate biomarkers, which predict the response to chemotherapy and may be used to select definitive therapy with less toxicity, are under investigation. To allow comparison of clinical trial results

and development of guidelines use of induction chemotherapy, it is essential that for response assessment radiological measurements are performed according to current guidelines using RECIST 1.1 (if only morphological imaging is performed) and PERCIST 1.0 criteria on accredited PET-CT scanners. Whereas RECIST criteria are historically focussed on a reliable assessment of any response after induction chemotherapy, new quantitative (functional imaging) techniques will attempt to predict response after subsequent chemoradiation using cut-off values. Optimal cut-off values can only be determined if in trials results are reported as continuous data and not only in categories of response.

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Table 1. Response assessment of induction chemotherapy in randomized clinical trials

Study	Tumors	Arms	n	Induction chemotherapy	Cycles	Criteria	Diagnostic technique	Result	Consequence of response
Head and Neck Contracts Program (1987)[22]	Resectable stage III/IV Oral cavity, hypopharynx, larynx	IC + S + RT	146	cisplatin bleomycin	1	WHO	clinical *	CR 8% PR 40%	no
		IC + S + RT + S	155						
			161						
Schuller et al (1988)[23]	stage III/IV HNSCC	IC + S + RT	82	cisplatin metothrexate bleomycin vincristine	3	WHO?	clinical *	CR 19% PR 51%	no
		S + RT	76				pathological	CR 21%	
Jortay et al (1990)[24]	T2/3 piriform sinus	IC + S + RT	89	vincristine bleomycin methotrexate	1	NA	macroscopic	no tumor shrinkage	no
		S + RT	98				microscopic	no histopathologic changes	
VA group (1991)[2]	stage III/IV larynx	IC + IC + RT	166	cisplatin 5-fluorouracil	2	WHO (without confirmation ≥ 4 weeks)	clinical *	CR 31% PR 54%	third cycle for responders RT for responders and S for non-responders
		IC + S					biopsy of primary tumor area	CR 64%	
		S + RT	166						
Richard et al (1991)[25]	T2-4 oral cavity / oropharynx	IC + S ± RT	112	vincristine bleomycin	12 days (intra-arterial)	WHO (without confirmation ≥ 4 weeks)	clinical *	oral cavity: CR + PR 48% oropharynx: CR + PR 41%	no
		S ± RT	110			CR: no living tumor cells PR: islets of living tumor cells NR: no modification of tumor cells	histopathology of surgical specimen	oral cavity: CR + PR 39% oropharynx: CR + PR 35%	
Paccagnella et al (1994)[26]	stage III/IV oral cavity / oropharynx/ hypopharynx/ paranasal sinus	IC + RT ± S	118	cisplatin 5-fluorouracil	1-4	re-evaluation after each cycle CR: total disappearance PR: ≥ 50% decrease in tumor volume	NA	CR: 31% PR: 49%	additional cycle (maximum total 4)
		RT ± S	119						
Volling et al (1994)[27]	T2/3 oral cavity / oropharynx/ hypopharynx/	IC + IC + RT	49	carboplatin 5-fluorouracil	1	WHO	endoscopy and clinical evaluation	CR 44% PR 18%	additional cycle (maximum total 3) RT for responders and S for non-responders
		IC + S							
		S + RT	47						
Maipang et al (1995)[28]	stage III/IV resectable HNSCC	IC + S + RT	30	cisplatin metothrexate bleomycin	2	WHO (without confirmation ≥ 4 weeks)	clinical or radiological *	CR 30% PR 43%	no
		S + RT	24				histopathology of surgical specimen	CR 23% PR 53%	
Lefebvre et al (1996)[9]	T2-4 piriform sinus	IC + IC + RT	97	cisplatin 5-fluorouracil	2	WHO (with for CR also mandatory complete recovery of larynx mobility)	endoscopic evaluation (CT recommended)	CR 54% PR 32%	additional cycle (maximum total 3) RT for responders and S + RT for non-responders
		IC + S + RT							
		S + RT	94						
Lewin et al (1997)[29]	mainly advanced	IC + RT ± S	215	cisplatin 5-fluorouracil	3	no evaluation	N/A	N/A	N/A
		RT ± S	208						

	HNSCC									
Richard et al (1998)[30]	T3 larynx	IC +	IC + RT	36	cisplatin 5-fluorouracil	2	>80% tumor regression	direct laryngoscopy	response 40%	additional cycle (maximum total 3) RT for responders and S + RT for non-responders
			S							
		S + RT		32						
Kohno et al (2000)[31]	stage III/IV oral cavity / pharynx	IC +	IC + RT	13	cisplatin etoposide mitomycin-C	1	WHO	clinical or radiological *	CR 31% PR 23%	additional cycle (maximum total 2) RT for responders and S for non-responders
			S							
		S		11						
Domenge et al (2000)[32]	T2-4 oropharynx	IC + S and/or RT		157	cisplatin 5-fluorouracil	1	WHO?	clinical CT (after third cycle) *	CR 20% PR 36%	after first: additional cycle unless tumor progression ≥ 25 after second: additional cycle if tumor regression
		S and/or RT		161						
Licitra et al (2003)[33]	T2-4 oral cavity	IC + S		98	cisplatin 5-fluorouracil	2	WHO	clinical *	CR 33% PR 49%	additional cycle (maximum total 3)
		S		97				pathological	CR 27% PR 18%	-
Urba et al (2006)[12]	stage III/IV larynx	IC +	C + RT	C	73	cis/carboplatin 5-fluorouracil	1	WHO	clinical *	CR + PR 75%	concurrent chemoradiation for responders surgery for non-responders
				S						
			S		19					
Vermorken et al (2007)[34]	stage III/IV unresectable HNSCC	IC + RT		177	docetaxel cisplatin 5-fluorouracil	1	WHO (without confirmation ≥ 4 weeks)	clinical		additional cycle (maximum total 4) unless progressive disease
				181	cisplatin 5-fluorouracil					
Lefebvre et al (2009)[10]	T3-4 larynx T2-4 hypopharynx	Alternating C + RT		224	cisplatin 5-fluorouracil	2	CR: complete disappearance of all macroscopic disease, with complete recovery of larynx mobility PR larynx: substantial regression of tumor volume, with complete disappearance of bulging valleculae, bulging of hypothyroid membrane, deep inavasion of preepiglottic space, and at least partial recovery of larynx mobility PR hypopharynx: substantial regression of tumor volume, with at least partial recovery of larynx mobility	CT / MRI endoscopy under general anesthesia	CR + PR 85%	additional cycle (maximum total 2) RT for responders and S + RT for non-responders
		IC	C+ RT	226						
			S + RT							
Lorch et al (2011)[35]	stage III/IV HNSCC	IC + CRT		255	docetaxel cisplatin 5-fluorouracil	3	no evaluation	N/A	N/A	N/A
				246	cisplatin 5-fluorouracil					
Lefebvre et al (2013)[36]	stage III/IV larynx /	IC	C+RT	60	docetaxel cisplatin	3	≥ 50% regression of primary tumor volume or recovered larynx	CT / MRI endoscopy under	85%	CRT for responders and S + RT for non-responders
			Ctx+RT	56						

	hypopharynx		S	23	5-fluorouracil		mobility	general anesthesia		

*: not further defined / specified; Ctx: cetuximab
NA not available
N/A not applicable

Table 2. Clinical studies using FDG-PET for response assessment after induction chemotherapy.

	Number of patients	Induction chemotherapy	Second scan (time after completion of chemotherapy)	Parameter	Lesion	Measure	Cut-off point	Reference standard	Accuracy
Brun et al (2002)[50]	10	1 cycle cisplatin, 5-FU	0-5 days	Metabolic rate	Primary tumor	Absolute	Median	Follow-up (median 3.3 years)	Local control < mean 96% ≥ mean 62% (p=0.007)
				SUVpeak					Local control < mean 91% ≥ mean 68% (p=0.07)
Chepeha et al (2009)[37]	12	1 cycle cis-/carboplatin, 5-FU	3 weeks	SUVmax (3x3 pixel)	Primary tumor	Visual estimation of decrease	50%	Endoscopy	Substantial agreement
Kikuchi et al (2011)[52]	15	1 cycle S-1 and CDGP	Mean 20.5 (14-31) days	SUVmax	Primary tumor and largest lymph node	Absolute	3.5	< 10% viable tumor in tumor bed in surgical specimen	Sens 71% Spec 89% PPV 71% NPV 89%
						Decrease	55.5.%		Sens 86% Spec 95% PPV 86% NPV 95%
Semrau et al (2015)[57]	47	1 cycle docetaxel, cisplatin	3 weeks	SUVmax	Primary tumor	Decrease	20%	>30% reduction in superficial tumor extension	Sens 97% Spec 56% PPV 90% NPV 83%
Wong et al (2016)[58]	20	2 cycles docetaxel, cisplatin, 5-FU	After first cycle	TLG	Primary tumor	Decrease	60%	Follow-up 3 months after completion of chemoradiation	Sens 73% Spec 80%
Gavid et al (2015)[56]	21	2-3 cycles docetaxel, cisplatin, 5-FU	After first cycle	SUVmax	Primary tumor	Decrease	30%	≥70% response with endoscopy after end of induction chemotherapy	Sens 69% Spec 63% PPV 75% NPV 90%
Yoon et al (2011)[54]	21	2 cycles S-1 and cisplatin	2-4 weeks	SUVmax	Primary tumor	Absolute	4.8	RECIST 2 months after completion chemoradiation	Sens 94% Spec 100% PPV 100% NPV 80%
						Decrease	65%		Sens 88% Spec 100% PPV 100% NPV 67%
Powell et al (2013)[44]	9	2 cycles cisplatin, 5-FU	NA	-	Primary tumor	Visual residual avidity	Yes / no	Follow-up and neck dissection	Sens NA Spec 89% PPV NA NPV 100%
					Lymph node				Sens 100% Spec 88% PPV 50% NPV 89%
Dalsaso et al	19	2-3 cycles		SUVmean	Primary	Decrease	-	4 biopsies from 4 separate sites	Pathologic complete

(2000)[49]		paclitaxicel and cisplatin			tumor			within pretreatment tumor area	responders mean reduction 82%, non- responders mean reduction 35% (p=0.01)
McCollum et al (2004)[51]	26	3 cycles cisplatin, 5-FU +/- docetaxel	NA	-	Primary tumor	Visual estimation of residual tumor	Yes / no	Biopsy of primary tumor site	Sens 100% Spec 65% PPV 27% NPV 100%
Abgral et al (2012)[46]	15	3 cycles docetaxel, cisplatin, 5-FU	Mean 15.8 ± 4.9 days after second cycle	SUVmax	Primary tumor	Decrease	EORTC criteria; metabolic response: SUVmax decrease >25%	1-year event-free survival (mean follow-up 14.3 ± 6.6 months)	Metabolic responders 0%, non-responders 27% survived 1 year
Yu et al (2014)[55]	28	3 cycles docetaxel, cisplatin, 5-FU	2-3 weeks	MTV	Primary tumor	Decrease	42%	Event free survival	Sens 67% Spec 90%
				TLG			55%		Sens 63% Spec 90%

TLG: total lesion glycolysis; MTV: metabolic tumor volume; SUV standard uptake value
Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value

Table 3. RECIST criteria

RECIST 1.1	
Target lesion	
- Measurable lesions	- Longest diameter of tumours or metastasis ≥1.0 cm - Short axis of lymph node metastasis ≥1.0 cm
- Non measurable	- Longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) - Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, bone metastasis without soft tissue component.
- Measurements	- Up to 5 lesions, with a maximum of 2 lesions per organ

Table 4. PERCIST criteria

PERCIST 1.0	
Target lesion requirements and selection at baseline	- SUVpeak measurement of the hottest lesion (known areas of iatrogenic or benign uptake should not be selected, e.g. Waldeyers ring, even when such a lesion has the highest SUVpeak) - SUVpeak ≥ 1.5 times SUVmean liver + 2 SD SUVmean liver In case of extensive liver metastases, SUVpeak ≥ 2.0 times SUVmean aorta + 2 SD SUVmean aorta - It should be reported when no target lesion can be selected because they are below the minimum threshold
Follow-up lesion selection	- SUVpeak meausurement of the hottest lesion (may not be the hottest tumour at baseline)
Response measurement and reporting	- Reporting of percentage of change in tumour metabolism with notation of number of weeks since treatment start = 100 x [SUVpeak follow-up target lesion – SUVpeak baseline target lesion] / SUVpeak baseline target lesion
Response categories	
Complete metabolic response	- SUVpeak < SUVmean liver and indistinguishable from surrounding background
Partial metabolic response	- ≥30% decrease of SUVpeak follow-up target lesion and: o at least 0.8 SUV units decrease of SUVpeak follow-up target lesion compared to baseline o no new FDG-avid lesions in a pattern typical of cancer o no increase in size > 30% of target lesion o no increase in size or SUVpeak of >30% in non target lesion
Stable metabolic disease	- increase or decrease of SUVpeak follow-up lesion <30% - increase of SUVpeak >30% and at least 0.8 SUV units
Progressive metabolic disease	- new FDG-avid lesion(s) in a typical pattern of metastasis