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Changes in Computed Tomography Perfusion (CTP) technique parameters following treatment in head and neck neoplasm

Vahid Changizi[1], *Hussein Abed Dakhli[2], Hedayatollah Soroush[3], Shadi Davari[4]
[1]*Professor, Department of Technology of Radiology and Radiotherapy, Allied Medical Sciences School, Tehran University of Medical Sciences, international campus, Tehran, Iran.*
[2]*Department of Technology of Radiology and Radiotherapy, Allied Medical Sciences School, Tehran University of Medical Sciences, international campus, Tehran, Iran.*
[3]*Msc, Medical imaging center, Imam Khomeini hospital. Tehran University of medical school, international campus Tehran, Iran.*
[4]*Phd Lecturer, Department of Medical Imaging, Allied Medicine Faculty, Tehran University of Medical Science, international campus, Tehran, Iran.*
*Corresponding author: *Hussein abed dakhil*

Abstract
Objective: *The purpose of this contribution is to define the computed tomography (CT) perfusion characteristics of head and neck squamous cell carcinoma through evaluating the changes in blood flow, blood volume, mean transit time and permeability surface products after treatment in patient with head and neck cancer and to get knowledge about importance of CTP for informing therapeutic decision about its applications and usefulness as an assessment tool to monitor and predict treatment responsiveness.*
Methods: *In this meta-analysis study, we were based on several previous studies dealing with the perfusion of head and neck neoplasm forming a subset of systematic review which attempts to collate empirical evidence that fits prespecified eligibility criteria to answer a specific research question. The number of patients included in this study was 389. We compared means of CTP parameters among various studies before and after treatment and used appropriate statistical test when needed. We discussed treatment response rates (percent) among reviewed articles and described main relevant characteristics of the patients.*
Conclusion: *This meta-analysis demonstrated the feasibility for routine clinical use of the perfusion CT using deconvolution analysis for the assessment of perfusion and permeability role in evaluating response to chemo-radiation in HNC of different stages.*
Keyword *: Meta-analysis, Computed Tomography Perfusion, Head and Neck Tumors, Chemotherapy.*

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I. Introduction

Head and neck cancers (HNC) represent about %5 of all malignancies newly diagnosed each year. Squamous cell carcinoma (SCC) is the most common histology, accounting for about 90% of these tumors [2]. According to the WHO Classification of Head and Neck Tumor, they are generic term that includes tumors arising within the anatomic confines of the nasal cavity and paranasal sinuses, nasopharynx, hypopharynx, larynx, trachea, oral cavity and oropharynx, salivary glands, odontogenic, ear and para ganglionic system [3]. SCC comprises about 95% of laryngeal malignancies. The majority originate from the supra glottic and glottis regions. The incidence in men is high (10/100,000 or more) in southern and central Europe, Uruguay, Argentina, southern Brazil, and among Blacks in the United States. The lowest rates (<1/100,000) are reported in South-East Asia and central Africa. The incidence in women is below 1/100,000 in most populations.. In this systematic review, we aim to find and assess previous research studies meeting the feasibility for routine clinical use of the perfusion CT using deconvolution analysis for the assessment of perfusion and permeability role in evaluating response to chemo-radation in HNC of different stages. A reasonable and accurate assessment of the practicability of CTP in HNC is currently an important goal since The obtained perfusion measurements seem to be sufficient for differentiating neoplastic from normal tissue as well as responders from nonresponders. Hence, it is rationale to use baseline CTP parameters values as predictors of therapy response, locoregional control and disease recurrence. These findings have potential clinical applications regarding noninvasive treatment monitoring in patients with HNSCC treated with nonsurgical organ preservation therapy. In addition, CT perfusion does have the potential to monitor treatment response by enabling noninvasive assessment of alterations in tumor vasculation and serving as a surrogate marker for tumor oxygenation. Accurate assessment

of tumor response could justify dose modulation or alternative treatment options if the functional parameters indicate non response among tumors treated with nonsurgical organ preservation therapy.

Perfusion CT Technique

The basic principle of perfusion CT is based on the temporal changes in tissue density following intravenous administration of iodinated contrast media. As a reflection of the nature of tissue vascularity, the chronological changes in tissue density are dependent on the iodine concentration. CTP allows quantification of the tissue vascularity by rapid sequential acquisition of images during the passage of contrast. Studying dynamics of perfusion parameters of tumor help in understanding the functional changes in tumor tissue induced by therapy to distinguish responders from non-responders [7].

In the study of head and neck cancer, CTP based software which generates the following perfusion parameters (table 1):

1. Blood flow (BF), expressed in mL/100g/min of tissue. It is the flow rate of blood through the vasculature in tissue region. BF includes flow information from large vessels, arterioles, capillaries, and venules as well as arteriovenous shunts, which are more common in neoplastic tissue than in healthy tissue.
2. Blood volume (BV), expressed in mL/100 g of tissue. It represents the volume of blood that flows within vasculature in a tissue region.
3. Mean transit time (MTT), expressed in seconds. It represents the mean time the blood takes to pass through the microvasculature from the arterial to the venous end. MTT is inversely correlated to BF.
4. Permeability-surface products (PS), expressed in mL/100g/min of tissue. It measures the product between the permeability and the total surface area of capillary endothelium in a unit mass of tissue (usually 100 g of tissue). It is considered as a surrogate marker of immature leaky vessels which are more common in neoplastic tissue [8-9].

Table 1 demonstrates the glossary of terms commonly used in CT perfusion.

Table 1. Glossary of terms commonly used in CT perfusion

Perfusion parameter	Definition	Marker (In Oncology)	Units
BF (Blood Flow)	Flow rate through vasculature in tissue region	Tumor vascularity Tumor grade	mL/100 g/min
BV (Blood volume)	Volume of flowing blood within a vasculature in tissue region	Mitotic activity and vascularity	mL/100 g
MTT (Mean transit time)	Average time taken to travel from artery to vein	Perfusion pressure	seconds
PS (Permeability Surface)	Total flux from plasma to interstitial space	Immature leaky vessels	mL/100 g/min
TTP (Time to peak)	Time from the arrival of the contrast in major arterial vessels to the peak enhancement		seconds
Perfusion	Flow rate through vasculature in tissue region	Tumor vascularity Tumor grade	ml/min/ml

Despite of presence of other imaging techniques allow assessment of tissue perfusion, CTP is particularly ideal for this purpose. This is primarily due to its widespread availability and better experience which permits its use in daily clinical practice. In addition, CTP shows a linear relationship between the iodine concentration and the density changes in the tissue which makes processing straightforward and simpler compared to MRI where the contrast-signal relationship and the quantification are problematic. The availability of commercial software makes multi-center assessment easily achievable as quality assurance becomes easier [10].

Physiology of contrast enhancement

After intravenous injection of the contrast media, the contrast distributes within the tissues resulting in increasing tissue density on CT. The contrast then distributes in the intra vascular and the extra vascular tissue compartment and the enhancement can be assessed in both two phases based on its distribution. In the initial phase, the enhancement is mainly due to the contrast distributed intravascularly. Later in the second phase as contrast passes to the extra vascular compartment across the capillary basement membrane, enhancement results from contrast distribution in both compartments. Thus, blood flow is the determinant factorin the initial phase, while in the second phase the enhancement will depend on the blood volume and the permeability of capillaries to the contrast medium [11].

Mathematical modeling techniques

It is possible for the temporal changes in the tissue attenuation to be recorded after intravenous injection of contrast by obtaining a series of image in quick succession in a particular tissue. Two basic

functional CT paradigms are measured; perfusion measurements and permeability studies. The perfusion's quantification is done using mathematical modeling techniques. The two most commonly used analytical methods for quantifying various perfusion parameters from the dynamic CT data are: Compartmental analysis and De-convolution analysis. for estimation of tissue vascularity and to correct for inter patient variations in bolus geometry, both methods require obtaining time attenuation data from the arterial input [5, 11-12].

Compartmental analysis

It is based on single or two compartment model. The single compartmental model is used to estimate the tissue perfusion considering intravascular and extra-vascular spaces as a single compartment. It is based on Fick's principle and calculates tissue perfusion. It estimates the perfusion either from the maximal slope or the peak height of the same tissue concentration curve that normalized to the function of arterial input. The two compartmental models are used to evaluate capillary permeability and blood volume. This model assumes the intravascular and extra vascular spaces as separate compartments and measures perfusion parameters using a technique called Patlak analysis which quantifies contrast passage from intravascular into the extra vascular space [5, 11-12].

Deconvolution analysis

It calculates the impulse residue function (IRF) for the tissue by using of arterial and tissue time-concentration curves. IRF is a theoretical tissue curve obtained from the direct arterial input assuming that the concentration of contrast is linearly dependent on the input arterial concentration when the blood flow is constant. Tissue perfusion will be reflected by the height of this curve after flow correction, while the area under the curve gives the relative blood volume. Distributed parameter model is used for the estimation of capillary permeability depending on extended de-convolution model [12].

Compartmental vs. Deconvolution analysis

Theoretical assumptions, susceptibility to noise and motion are the main aspects of difference between both the techniques although preliminary results have shown that they are broadly equivalent. Deconvolution assumes that the shape of IRF will be a plateau with a single exponential wash-out which might not be suitable for organs such as spleen and kidney which have complex microcirculations. While compartmental analysis assumes that the bolus of contrast media has to be retained within the organ of interest at the time of measurement which may result in underestimation of perfusion values with large bolus injectionor in organs with rapid vascular transit. Hence, it is preferable for organs with complex circulatory pathways to use compartmental analysis. Inclusion of the complete time series of images in calculation enables deconvolution methods to tolerate greater image noise and to be appropriate for measuring lower levels of perfusion (< 20ml/min/100ml). This is particularly beneficial to accurately estimate lower perfusion values typically seen in tumors following treatment response. After that, there is chance of image mis- registration due to motion of the patient and calculation of all acquired images. In compartmental analysis, perfusion measured by using the base line image and the image immediately before and after the time of maximal enhancement rate and hence patient motion are not significant[11].

Acquisition protocols

The typical perfusion protocol consists of a baseline image acquisition without any contrast enhancement followed by a dynamic image acquisition sequentially performed after injection of contrast media. Depending on the physiological parameter to be measured, the dynamic image acquisition includes a first pass study or a delayed study or both. The first pass study comprises of the images which are acquired in the initial 45-60 sec and are used for assessing blood flow (perfusion) and blood volume. To measure vascular permeability, a delayed phase which can range from 2 to 10 minis necessary to be included (figure 1).

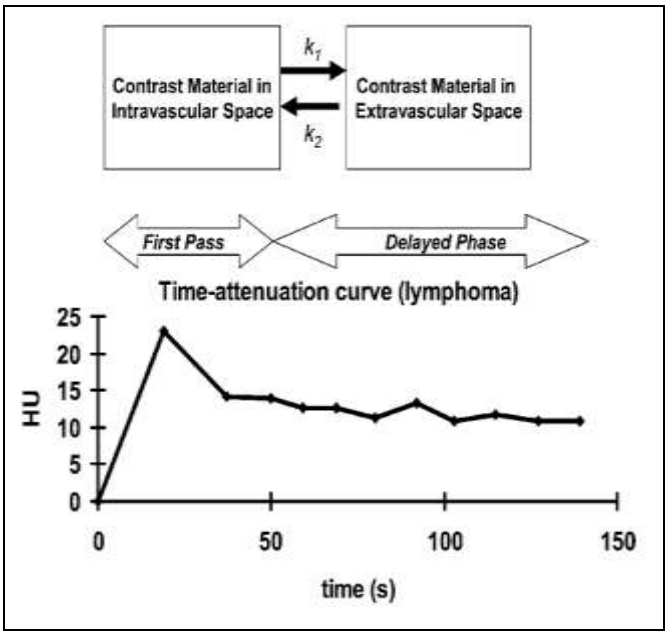


Figure 1. Time–attenuation curves from tumors are determined by the contrast material in the intravascular and extravascular compartments. During the first pass, the contrast material is predominantly intravascular and contrast enhancement reflects perfusion and blood volume. Delayed enhancement is determined by the passage of contrast material into and out of the extra- vascular space, as determined by rate constants k1 and k2[12].

The choice of technique also depends on the mathematical modeling method has used (table 2). Being less sensitive to noise, deconvolution method allows the use of a lower tube current and scanning with higher temporal resolution. The typical perfusion protocol for measurement of perfusion and blood volume is image acquisition for a total duration of 40- 60sec with 1 sec images every 1 second after injection of 40-50ml of contrast at a rate of 4-7 ml/sec with a tube current of 50-100mAs. For permeability measurements, a two-phase study is indicated based on the distributed parameter model. The first phase is as described above followed by a second phase which involves acquisition of 1 sec images acquired every 10 seconds for 2 minutes.

Table 2. Acquisition and processing parameters for three illustrative perfusion CT protocols for the assessment of tumor vascularity [12]

Criteria	Protocol 1	Protocol 2	Protocol 3
Contrast media Concentration	370 mg ml^{-1}	370 mg ml^{-1}	370 mg ml^{-1}
Volume	40 ml	50 ml	100 ml
Injection rate	4–7 ml s^{-1}	7–10 ml s^{-1}	4 ml s^{-1}
Acquisition type	Single location	Single location	Multiple spiral
Slice thickness	4*5mm	2*10 mm	20*3 mm
No. images	60	15	6
Image frequency	Every 1 s	Every 3 s	Every 20 s
Tube current	50–100 mAs	100–250 mAs	100–250 mAs
Analysis method	Deconvolution for perfusion and blood volume	Compartmental analysis for perfusion and blood volume	Standardized perfusion value Patlak analysis for permeability and blood volume
Advantages	Good temporal resolution High spatial resolution	Low image noise	Large volume coverage
Disadvantages	Image noise Limited volume coverage	Reduced temporal resolution Limited volume coverage	High spatial resolution Poor temporal resolution

Presence of image noise in the compartmental model results in miscalculation of perfusion values, hence a higher mAs value with lower image frequency is preferred. For compartmental analysis for measurement of perfusion and blood volume, the typical image acquisition sequence is for a total duration of 40-60sec with 1 sec

images every 3-5 sec after injection of 40-50ml of contrast at a rate of 7-10 ml/sec with a tube current of 100-250mAs. Two compartmental model is used (Patlak analysis technique) for the permeability measurements, which includes acquisition of images every 10- 20 secs after injection of 100 ml of contrast at a rate of 4 ml/sec with a tube current of 100-250mAs[5, 12-13].

CTP application in Oncology

Perfusion CT is emerging with increasing applications in oncology with clinical evidence in several areas. These include (a) to differentiate between benign and malignant ones (b) detection occult malignancy (c) staging of cancers and providing prognostic information and (d) to monitoring therapeutic effects chemoradiation and antiangiogenic drug[11].

Imaging Biomarkers

The development of a tumor blood supply through the processes of neovascularization, which is called angiogenesis, is essential for the growth of tumors. Angiogenesis also determines the ability of tumors to metastasize and highly vascularized ones have been shown to be associated with a poor prognosis. The basis for using perfusion CT in oncology is that the microvascular changes in angiogenesis are reflected by increased tumor perfusion in vivo (figure 1)[5].

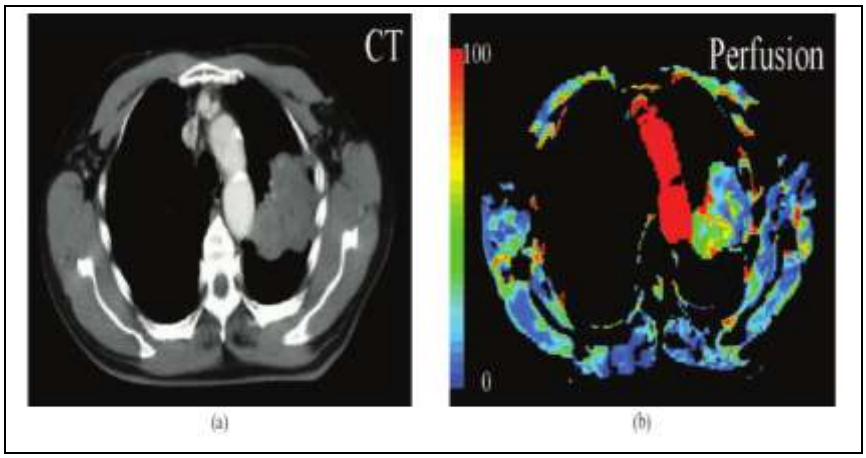


Figure2: Perfusion CT of a lung nodule obtained using the deconvolution method. (a) CT image, (b) perfusion image. Note the heterogeneous distribution of perfusion within the nodule[5].

Microvascular density (MVD) which is direct pathological marker of angiogenesis is considered as predictor of response in head and neck cancers. MVD requires endoscopic biopsy and is an invasive procedure accompanied by its own risks. CTP is a measurement of intra tumoral MVD which has a prognostic value[14]. It is justifiable for that CT perfusion (CTP) has recently been used to obtain measures of tumor vascular physiology and hemodynamic as surrogate biomarker. This technique, starting from brain ischemia and brain tumor evaluation, quickly became an effective, simple and reliable method for the assessment of neo-angiogenesis, which is typical for tumors. During recent years, CTP has been widely used to detect, stage and predict the behavior of cancer and to assess the response to radio and chemotherapy[6-7, 14-17]. CTP has emerged as a non-invasive functional imaging tool providing quantitative parameters regarding angiogenesis and tumor perfusion. CTP offers the indisputable advantages of being noninvasive, relatively inexpensive and widely available technique which can predict the response, monitor the effects and assess long term treatment outcome in head and neck carcinoma[12]. CT perfusion has been validated and has shown to be feasible technique to show changes of perfusion to anti-angiogenic therapy (Figure 3)[11, 18].

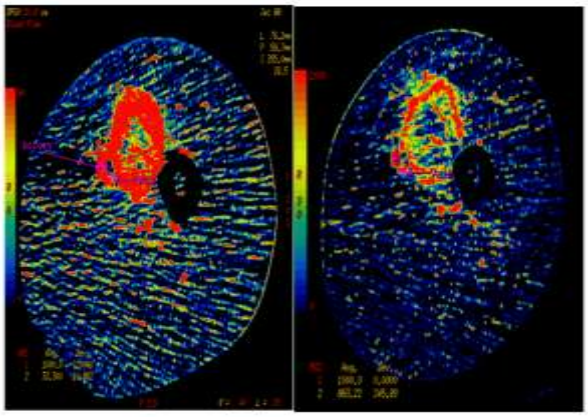


Figure 3. Pre and post antiangiogenic CTp images in a 65 yr old male with malignant fibrous histiocystoma of the thigh. (A)Colored perfusion map of blood flow at baseline before antiangiogeneic treatment shows increase tumor blood flow (110ml/100g/min). (B) Colored perfusion map after treatment shows significant reduction in tumor blood flow (60ml/100g/min).

II. Material And Methods

For this systematic review, Embase, the Cochrane library, MEDLINE, Pubmed, Elsevier, Springer, free journals and Google scholar were searched using the search terms head and neck neoplasm, head and neck cancer combined with computed tomography perfusion, CTP, parameters, treatment, chemotherapy, radiotherapy and response.

Only original articles that performed during the years 1990 to 2016 presented in English language that relevant to our objectives were considered for inclusion. References of all retrieved articles were manually searched for additional relevant manuscripts. Studies found through these search terms were assessed for potential eligibility by reading the abstracts first and then applying inclusion and exclusion criteria.

Included articles were only those in which head and neck CTp was performed at baseline and prior to treatment; chemo or radiotherapy. To be eligible for this review, we decided that a study should consist patients with newly diagnosed or recurrent, histologically proven head and neck cancer undergoing chemo or radiotherapy who were imaged using CTP.

Studies were not excluded if other imaging modalities were performed parallel to CTP in order to evaluate treatment response. After this initial assessment, the publications were summarized using a standard extraction form. Extracted data included: first author, year of publication, study design (retrospective or prospective), population size, mean patient age and range, cancer stage at inclusion, cancer histology, treatment regimen, imaging response assessment.

While scoring the extraction forms in consensus, some studies were excluded if the study outcome proved not to contain information on response evaluation by CTP. All reported P-values ≤ 0.05 were considered statistically significant. The large heterogeneity observed in the included studies precluded us from pooling data, which is why we chose to use descriptive statistics in this review.

We chose some variables in the referenced articles to be reviewed to answer our research questions.

These variables were:

1. Article study type: like clinical trial, systematic review, RCT (Randomization control trial), case control, cross sectional studies and case reports.
2. The outcomes of patient was considered in review regarding their response to treatment.
3. Values of CTP parameters.

We compared means of CTP parameters among various studies before and after treatment and used appropriate statistical test when needed.

We discussed treatment response rates (percent) among reviewed articles and described main relevant characteristics of the patients.

III. Results:

1. Study Selection

The computerized and manual search retrieved a total of 175 articles. After assessing the titles and abstracts, 42 articles were found to be potentially relevant. After the full text assessment, 13 studies (table 3)

met the inclusion criteria of having CTP parameters values pre and post therapy, so they were submitted to further in depth reading, summarization and comparison in this study.

2. Study Description and Patients Characteristics

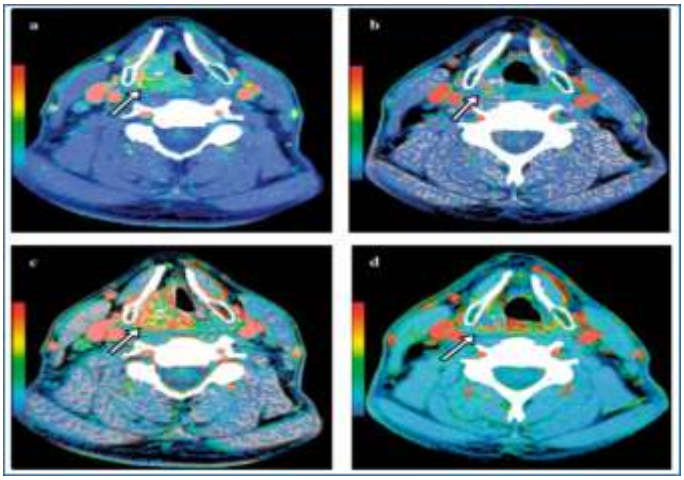
Of the 13 included studies in comparison, all were prospective. A total of 389 patients were involved in these studies aged 35 to 88 years. Among those patients, the tumor locations included oral cavity, nasopharynx, larynx, oropharynx, laryngopharynx, hypopharynx and upper earodigestive tract. All cancers were HNSCC staged I to IV according to WHO classification [3]. The characteristics of included studies are listed in table 3.

Table 3. Main characteristics of included studies

Author	Year	Study type	Patients No.	M/F	Age:Mean (±SD) OR Median (range)	Cancer site/type	Cancer stage
Hermans et al	2003	P	105	93/12	56 (36-82)	HNSCC	I-IV
Gandhi et al	2006	P	9	6/3	56.3 (49-72)	HNSCC	III-IV
Zima et al	2007	P	17	11/6	55.4 (40-80)	Upper EDTSCC	III-IV
Bisdas et al	2009a	p	19	17/2	55.6 ± 9.2	Upper EDTSCC	III-IV
Bisdas et al	2009b	P	21	12/9	57 ± 11	HNSCC	II-IV
Petralia et al	2009	P	25	22/3	59 (48-71)	Upper EDTSCC	III-IV
Bisdas et al	2010	P	84	62/22	59 (35-88)	Upper EDTSCC	II-III
Surlan et al	2010	P	20	19/1	61 (40-74)	HNSCC	III-IV
Truong et al	2011	P	15	12/3	58 (45-68)	HNSCC	III-IV
Tuntiyatorn et al	2014	P	12	7/5	51.8 ± 11.7	NPC	-
Pietch et al	2015	P	13	12/1	63 (44-78)	HNCSCC	III-IV
Rana et al	2015	P	24	23/1	57.9 ± 4.5	HNCSCC	III-IV
Ursino et al	2016	P	25	-	-	HNSCC	III-IV

BF = blood flow; BV = blood volume; PS = capillary permeability surface product; MTT = mean transit time; RT = radiotherapy; CRT = chemoradiotherapy

Scarce studies investigated the value of tumor CT perfusion in predicting response to chemoradiotherapy among patient with HNC [20]. This is based on the theory that changes produced by radiotherapy and chemotherapeutic agents on tumor vascularity can be identified by changes in CT perfusion parameters. Treatment induced reduction of micro-vessels inside the tumor could be identified as a decrease of BV values while a decrease of BF could indicate a reduction of low resistance flow arteriovenous shunts in the microvasculature. Reduction in hyper-permeable capillary bed could be expressed with a decrease of PS values [21] (Figure 4 a-h).



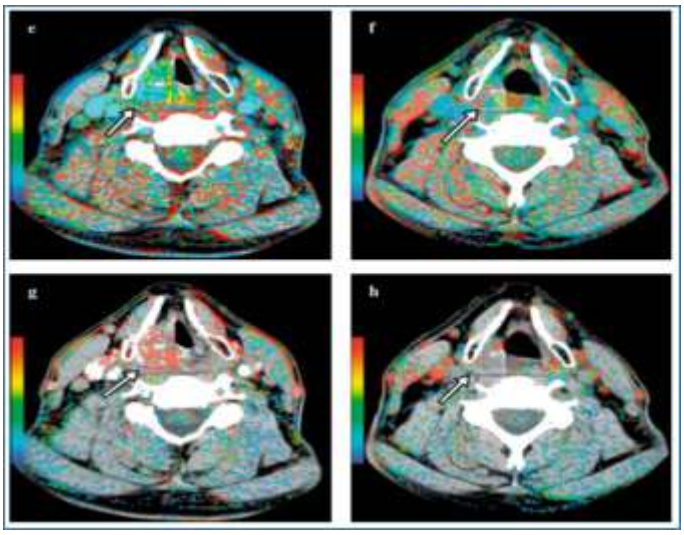


Figure.4 a-h A 61-year-old patient with invasive poorly differentiated squamous cell carcinoma of the right pyriform sinus (white arrow with black border). CTP performed before (a,c,e,g) and after (b,d,f,h) induction chemotherapy. a,b Color maps for BF before (a) and after (b) induction chemotherapy: tumor shows a greater presence of yellow and red nuances before therapy and a greater presence of green and blue nuances after therapy. This indicates a decrease in BF after therapy. c,d Color maps for BV before (c) and after (d) induction chemotherapy: tumor shows a greater presence of yellow and red nuances before therapy and a greater presence of green and blue nuances after therapy. This indicates a decrease in BV after therapy. e,f Color maps for MTT before (e) and after (f) induction chemotherapy: tumor shows a greater presence of green and blue nuances before therapy and a greater presence of yellow and red nuances after therapy. This indicates an increase in MTT after therapy. g,h Color maps for PS before (g) and after (h) induction chemotherapy: tumor shows a greater presence of yellow and red nuances before therapy and a greater presence of green and blue nuances after therapy. This indicates a decrease in PS after therapy.[21]

Gandhi et al. 2006 [15] studied nine patients with advanced (stage 3 or 4) SCCA of the oropharynx in a prospective trial in which induction chemotherapy was used to assess the tumor response. Patients underwent direct laryngoscopy and CTP before and three weeks after one cycle of chemotherapy. In the responder group, they noted the following changes in mean pre- and post-induction chemotherapy values: mean BF, 114.2 mL/100 g /min (pre-induction) to 45.1 mL/100 g/min (post-induction); mean BV, 5.11 mL/100 g to 3.1 mL/100 g; mean PS, 25.6 mL/100 g /min to 18.3 mL/100 g / min; mean MTT, 4.9 seconds to 8.0 seconds. In the non-responder group, they had noted these changes: mean BF, 56.9 mL/100 g/min to 75.9 mL/100 g/min; mean, BV 2.7 mL/100 g to 4.71 mL/100 g; mean PS, 24.1 mL/100 g/min to 23.7 mL/100 g/min; mean MTT, 4.3 seconds to 5.34 seconds. Higher baseline values of BV showed significant correlation with endoscopic tumor response ($P < 0.05$).

Petralia et al. 2009 [22] in a trial to assess the potential of CTP for monitoring induction chemotherapy in patients with SCCA of the upper aerodigestive tract, they investigated 25 patients underwent CTP and volumetric CT before and after induction chemotherapy. In 17 patients classified as responders, a significant reduction in both tumor BF ($P = 0.003$) and BV ($P = 0.014$) and significant increase in MTT ($P = 0.04$) after therapy were observed. The median value decreased from 73.2 (baseline) to 34.5 mL/100 g per minute (post-therapy) for BF and from 5.6 (baseline) to 3.7 mL/100 g (post-therapy) for BV, whereas median MTT increased from 6.2 (baseline) to 8.3 seconds (post-therapy). Variable changes, which are not statistically significant ($P = 0.24$), have been found in PS, with median values decreasing from 13.8 (baseline) to 9.4 mL/100 g per minute (post-therapy). Eight of the 17 responders were classified as complete responders (CRs), and 9 were classified as partial responders (PRs). The investigators found a significant decrease in BF ($P = 0.008$) and BV ($P = 0.008$) at the post-therapy CTP in CRs, whereas only minor changes, which are not statistically significant, they observed in BF and BV after therapy in PRs.

Truong et al. 2011 [23] assessed the loco-regional control (LRC) in 15 patients with HNSCC receiving definitive RT who underwent serial CTP before RT; at weeks two, four, and six of RT; and six weeks after RT. They found that BF measurements at baseline were significantly higher in patients who achieved LRC (118.0 mL/100 g/min) compared with loco-regional failure (LRF) (53.4 mL/100 g/min, $P = 0.004$). Similarly, BF measurements at week two (12.72 Gy) of RT were significantly higher in patients who achieved LRC (135.8

mL/100 g/min) compared with LRF (43.9 mL/100 g/min, P <0.001). PS measurements at baseline were significantly higher in patients who achieved LRC (16.6 mL/100 g/min) compared with LRF (7.7 mL/100 g/min, P = 0.02). Also PS measurements at week two (12.72 Gy) of RT were higher in patients who achieved LRC compared with those with LRF, though the difference between the two groups trended toward statistical significance (P = 0.098). At week 2 of RT (12.72 Gy), tumor BF parameters showed a 27.5% increase compared with pretreatment BF values in patients who achieved LRC versus an 18.1% decrease from pretreatment BF values (P= 0.046) for those with LRF. For patients with both LRC and LRF, BF appeared decreased 6 weeks after completion of RT compared with their baseline values. The percentage change in BV increased in patients with LRC compared with those with LRF at week 2 of RT compared with baseline (P = 0.053). MTT parameters were not found to be significantly different between the 2 groups of patients, and no significant patterns were identified. The percentage change at week 2 in PS was noted to be higher in patients with LRC compared with patients with LRF (P = 0.106).

Surlan-Popovic et al. 2010 [24] prospectively analyzed differences in perfusion and tumor volume values of 20 patients with HNSCC during chemoradiotherapy and between responders and nonresponders groups. They observed a significant trend of reduction in the BF and BV values compared with the baseline values (P = 0.04) in responders after 40 Gy which was more pronounced after 70 Gy for BF (p= 0.01). Whereas, in non- responding patients, the BF and BV values showed a nonsignificant trend of elevation (P= 0.06). They reported nonsignificant changes in MTT values in both groups in different three points of time. In addition, PS values in the responders were almost stable after 40 Gy and non-significantly increased after 70 Gy (P = 0.08), while in nonresponders, they presented an elevation at 40 Gy, which was continued also after 70 Gy (P= 0.03).

Ursino et al. 2016 [25] aimed to evaluate changes in CTp parameters of the HNC in 25 patients underwent a PCT at baseline, three weeks and three months after radiochemotherapy (RCT). They noticed a significant reduction of all CTp parameters in the three-week post-RCT scan (p<0,001) except MTT, with respect to the baseline one. In particular, a significant reduction of all the CTp values, including MTT (from 6.18 sec to 2.24 sec; p=0.001), were significantly lower than the baseline values in the three-month CTp (p<0,001). (Figure8).

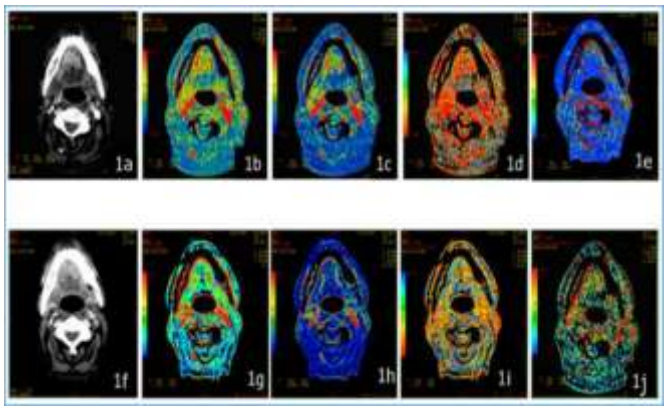


Figure 8. Early radiologic response assessment in a 75-year-old patient with squamous cell carcinoma of the oral tongue treated with radiochemotherapy. (a) Pre-treatment morphologic CT image obtained from first-pass PCT dataset. (b) BV, (c) BF, (d) MTT, and (e) PS color maps show altered lesion perfusion compared to the surrounding tongue tissues. (f) Post-treatment morphologic CT image obtained from first-pass PCT dataset. Quantitative measurement of pre-treatment PCT parameters revealed BV=3.40 mL/min, BF=84 mL/min per 100 g, MTT=2.74 s, and PS=12.3 mL/min per 100 g, respectively. (g) BV, (h) BF, (i) MTT, and (j) PS color maps show normalization of lesion perfusion 3 weeks after RCT treatment. Quantitative measurement of posttreatment PCT parameters revealed BV=2.03 mL/min, BF=34 mL/min per 100 g, MTT=6.74 s, and PS=9.25 mL/min per 100 g, respectively.

Hermans et al. 2003 [26] investigate the value of CT-determined tumor perfusion as a predictive factor of local and regional failure in 105 HNC patients treated by radiotherapy. They set a median perfusion value (83.5 mL/min/100 g) as cutoff point to stratify the patient to two groups, either with local failure or control.
The perfusion was calculated by dividing the slope of the tumor time–density curve by the maximal value in arterial density during the first pass of the contrast. They found that the patients in the high- perfusion group showed a significantly higher local control rate (p < 0.05) (Figure 9).

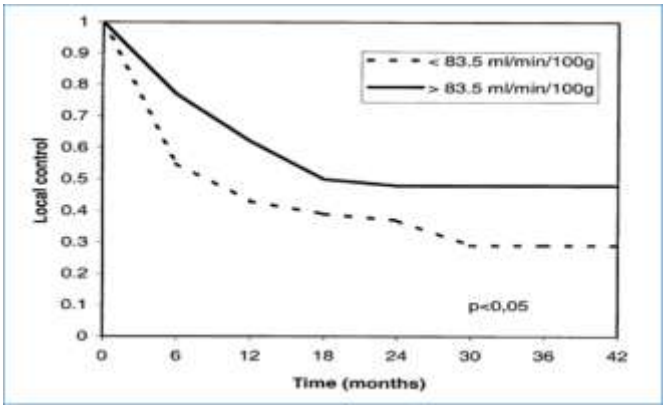


Figure 9. Local control vs. perfusion rate (all patients [n _ 105], stratified into two groups according to the median value), plotted over time after start of radiotherapy. [26]

Zima et al. 2007 [7] prospectively assess whether pretreatment evaluation of primary tumor with quantitative CTp measurements predicted response to induction chemotherapy. They enrolled 17 patients with advanced SCC of upper aerodigestive tract and defined functional response as >50% reduction in tumor volume as assessed by endoscopy. They realized that 12 responders had higher values of pretherapy BV, BF, and CP compared with five nonresponders. There were statistically significant correlations between higher values of BV (P= 0.004) and BF (P= 0.03) and endoscopic tumor response. The correlation between lower values of MTT (P= 0.29) and higher values of CP (P= 0.07) with tumor response were not significant.

Bisdas et al. 2009a [27] assessed response to neoadjuvant chemotherapy in 19 case of oropharyngeal SCC by correlating CTp parameters measured at baseline and tumor volume evaluated endoscopically according to radiologic criteria (RECIST criteria) [28]. Patients with complete response and partial response were classified as responders.

The baseline mean BF for the 19 subjects was 72.3 ± 32.0 mL/min/100 g (95% CI, 69.5–75). The baseline BF in the nonresponders group (8 patients) was 69.4 ± 31.6 mL/min/100 g (95%CI, 66–72.3) compared to that of responders group (11 patients) was 77 ± 32.05 mL/min/100 g (95% CI, 72.5–81.4), (P= 0.002).
The pooled baseline BV was 5.5 ± 2.5 mL/100 g (95% CI, 5.3–5.7). The baseline BV in the responder group was 6.3 ± 2.7 mL/100 g (95% CI, 6–72.6). The baseline BV in the nonresponder group was 4.1 ± 1 mL/100 g (95% CI, 4–72.3), (P<0.001). The initial pooled MTT was 7.3 ± 2.3 s (95% CI, 7.1–7.5). The baseline MTTin the responders group was 5.5 ± 2 s (95% CI, 5.2–5.7) compared to that in nonresponders group of 8.4 ± 1.7 s (95% CI, 8.2–8.6), (P<0.001). The initial average PS in all subjects was 10.8 ± 0.3 mL/min/100 g (95% CI, 10.5–11). The baseline PS in the responders group was 12.6 ± 1.7 mL/min/100 g (95% CI, 12.3–12.8) compared to that in nonresponders group of 9.8 ± 3.1 mL/min/100 g (95% CI, 9.5–10.1), (P<0.001). There was a statistically significant difference between the 2 groups regarding all CTp parameters assessed in this study.

Bisdas et al. 2009b [29] assessed whether CTp may predict outcome in 21 chemoradiated patients with oral cavity, oropharynx, and hypopharynx SCC after surgical excision: they applied a new analysis on the region of interest- derived CTp values, namely, the maximum BF, BV, and PS, as well as the minimum MTT values, trying to avoid the considerable intratumoral variation covered with mean values. Both mean perfusion values and BF max, BV max, and BS max were significantly different between patients with and without tumor recurrence ($p < 0.04$). Also, the authors underlined the predictive value of PS and MTT. In particular they found a relative risk of recurrence about 14 time higher in patients with lower than the median BS mean values, which is apparently in contrast with the results of other studies demonstrating a significantly shorter disease-free survival in patients with high intratumoral microvessel density [31]. According to the authors these findings confirm the absence of any clear relationship between microvascular density and PS values [32].On the other hand the predictive role of MTT values may be attributed in part to leaky tumor vessels, which lead to improved oxygenation.

In a large series of 84 patients with advanced HNSCC who underwent CTp prior to concomitant chemoradiotherapy, Bisdas et al. 2010 [30] found that BF and PS values were significantly higher in patients who had no recurrence than in those with local failure ($p \leq 0.02$). The BF and PS were predictive ($P< 0.001$) but BV and MTT held no significant predictive values for local tumor control. The patients with high BF and PS had a longer local tumor control than the patients with hypoperfused tumors ($P = 0.001$). (Figure 12).

Furthermore a simultaneous visual evaluation of the BF and the BV parametric maps showed that the presence of a mismatch (>30% of the examined lesion extent) between the color-encoded maps correlates with shorter life expectance ($p = 0.01$) and smaller recurrence-free survival ($p = 0.03$) . This approach is based on the rational that a considerable mismatch, more evident in locally advanced tumors, may indicate a heterogeneous

pattern of vascularisation, which may lead to a cascade that influences cellular phenotypes and presents with therapy resistance [31].

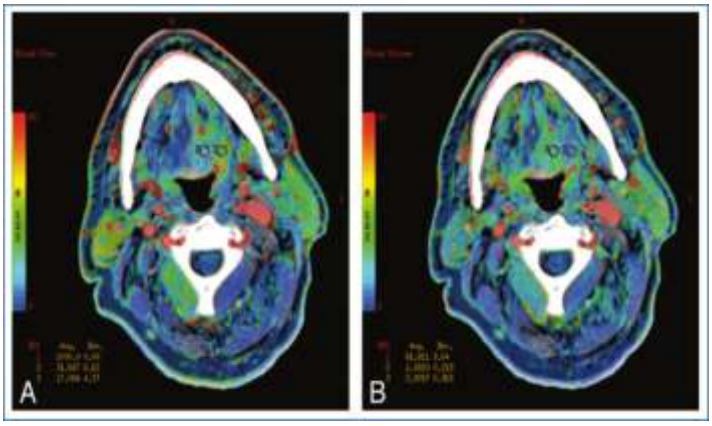


Figure 12. BF (A) and BV (B) parametric maps of a 69-year-old man with SCCA of the oropharynx on the left side. Visual analysis (as also confirmed by the region-of-interest measurements) shows 2 functionally different tumor compartments regarding BF and BV properties and, thus, a BF-BV mismatch. [30]

Pietsch et al. 2015 [32] prospectively studied 13 patients with HNSCC underwent radio and/or chemotherapy to proof predictive role of CTP in assessment of response. They compared pre and posttherapeutic mean CTP-values and found that patients with recurrent disease had significantly higher initial CTP-values: BF 267.4 ml/100mg/min, BV 40.9 ml/100 mg, MTT 8.2 sec, compared to the recurrence-free patients: BF 171.2 ml/100 mg/min, BV 8.4 ml/100 mg and MTT 6.1sec.

Rana et al. 2015 [33] conducted a prospective study among 24 patients with HNSCC registered for chemoradiotherapy (CRT). CTp data were acquired at baseline, on completion of 40 Gy and 66 Gy of chemoradiation. They stratified the treatment outcome as complete response and non-response (partial responders/stable disease/progressive disease) using RECIST 1.1 criteria and compared all perfusion parameters at baseline, 40 Gy and 66 Gy of CRT between responders and non-responders. They defined the perfusion parameters as high (>median value) and low (≤median value) to analyze association between perfusion parameters and therapy outcome and stratified the patients in four different patterns of combination of perfusion parameters. They revealed that BF and BV decreased and Mean Transit Time (MTT) increased significantly ($p < 0.05$) at 66 Gy among responders to CRT as compared to non-responders. No significant changes in PS value in different groups. Patients with high BF (>106 ml/100 g/min) at baseline were five times more likely ($p = 0.004$) to respond to treatment as compared to those with low BF. BF of ≥85 ml/100 g/min was predictor of complete response to treatment. There was 100% response to treatment in the perfusion parameter combination of high BF and low PS irrespective of the stage of HNSCC. BF was found to be 83.3% predictive of complete response. Other perfusion parameters were not.

Tuntiyatorn et al. 2014 [34] prospectively studied 12 patients with histologically proven NPC who underwent pretreatment CTP with parameters followed by CECT at three months after complete concurrent chemo-radiotherapy or radiotherapy. They assessed the response to therapy by RECIST guideline, classified into non-response and complete response group. They demonstrated that BV, BF, and permeability had a positive correlation with reduction degree of primary tumor volume. In addition, all parameters had a trend to be higher in complete response group compared with non-response group. PS was an excellent CTP parameter to discriminate between two group with optimal cutoff value of 45 ml/100 g/min, which showed 100% sensitivity and 90% specificity.

IV. Discussion

In this systematic review, we aimed to evaluate the changes in CTP parameters following radio/chemotherapy among patients with head and neck cancer. CT perfusion has been studied in patients with head and neck SCC for the diagnosis and characterization of disease and the prognosis and evaluation of its response to treatment. However, up to our knowledge, there is no meta-analysis study done previously aimed to evaluate CTp parameters changes pre and post therapy. In our systematic search we found only one recent review summarized the technique and clinical applications of CTp of head and neck cancer [20] approaching nine articles only. While in this review we reached and analyzed 13 relevant studies, adding four more recently published articles, 2014 and beyond. Perfusion CT relies on the passage of iodinated contrast material through a region of interest to produce schanges in attenuation, which may be used as markers of microvascular blood flow [35]. A kinetic model analysis of these changes in attenuation allows the derivation of several physiologic

parameters, including BF, BV, MTT and permeability. In a small group of nine patients treated with induction chemotherapy, Gandhi et al. 2006 [15] found a positive correlation between BV pretreatment values and tumor response assessed by endoscopy. They found that a decrease more than 20% in BV values after three weeks of therapy is able to predict a reduction of cancer volume greater than 50%.

Petralia et al. 2009 [22] confirmed the relevance of CTp parameters in monitoring the response to chemotherapy. They found a significant correlation between the percent change in BV and BF values and the percent reduction of tumor volume after three cycles of induction chemotherapy. Their results appear to be more reliable since they use, as response quantification, tumor volume assessed by CT instead of the endoscopy standard which is an operator-dependent technique. Serial fluctuations in perfusion parameters of HNSCC during a course or radiotherapy were prospectively evaluated by Truong et al. 2011 [23], by using CTp to provide information about the periodical changes in tumor oxygenation produced by radiotherapy. Pretreatment tumor BF and PS was higher in patients who achieved LRC compared with those with LRF. Furthermore, authors demonstrated that an increase in BF during the first two weeks of radiotherapy is able to predict LRC, with a decrease in both groups after six weeks of radiotherapy compared with the baseline values, suggesting that a higher BF in tumor tissue at the baseline and during the early course or radiotherapy predicts a better tumor control.

Surlan-Popovic et al. 2010 [24], in a series of 24 patients with locally advanced HNSCC, demonstrated that the changes of CTp parameters during the course of treatment might predict tumor response to cisplatin-based chemoradiotherapy. In particular responders presented a significant reduction of BF values after 40 Gy which was more pronounced after 70 Gy and a significant reduction of BV values after 40Gy with a plateau after 70Gy. MTT and PS values showed nonsignificant modifications. On the contrary in nonresponders BF, BV, and PS values showed a nonsignificant increase after 40Gy. The possible explanation given by the authors to these findings is that the dynamics in CTp parameters are mainly related to the cytotoxic effects of radiotherapy to the vascular endothelium which is more effective than the little antivascular action of cisplatin-based chemotherapy. To explain the increase of perfusion parameters values observed in nonresponders group, authors hypothesized that ionizing radiation therapy may produce the upregulation of VEGF which in turn promotes survival of endothelium in residual tumor tissue and consequently radiation resistance [36].

Results obtained by Ursino et al. 2016 [25] showed a significant reduction of all CTp values, except MTT, already as early as three weeks after treatment, thus demonstrating a strong effect of radiochemotherapy (RCT) on such parameters. Therefore, MTT was the least sensitive parameter to demonstrate the effect of RCT, as it took longer (three months) for its reduction with respect to baseline to reach statistical significance. On the contrary, BV, BF and PS resulted highly sensitive parameters, as they exhibited a significant reduction already at three weeks post-RCT, with a trend towards further reduction in the three-month CTp scan versus the three-week one. The researchers had related the reduction in the BV and BF values to the damage induced by RCT on the intratumor microvasculature and low-resistance flow of neoplastic vessels. Whereas the observed decline in the PS values explained by reduced neoangiogenesis. However, they interpreted the significant reduction in MTT at the final treatment session as due to the high rate (68%) of complete response based on the standard RECIST criteria that precluded a real computation of MTT value.

In a series of 105 patients with HNSCC treated with definitive radiotherapy, some associated with adjuvant chemotherapy, Hermans et al. 2003 [26] found that CTp parameter are independent predictors of local control together with T stage. Inparticular patients with a low perfusion pretreatment value showed a statistically significantly higher local failure rate than those with a high perfusion value ($p < 0.05$), presumably due to a more extensive degree of hypoxia in low-perfused tumor and therefore characterized by low radiosensitivity (Figure 16).

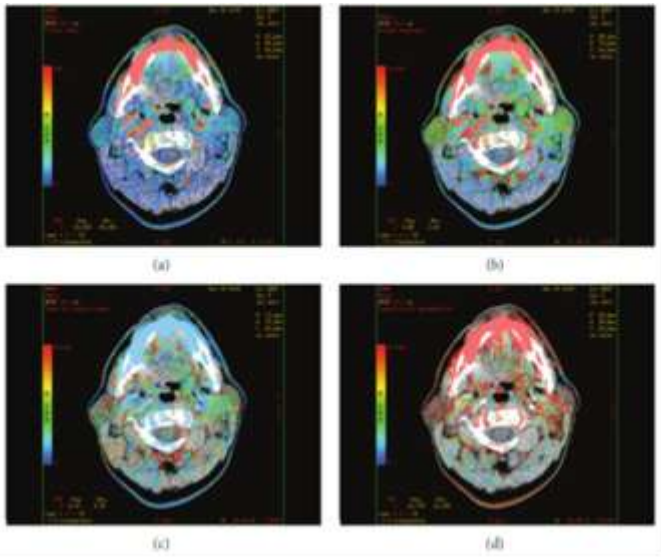


Figure 16. Squamous cell carcinoma of the oropharynx in a nonresponder patient. The functional maps of BF (a), BV (b), MTT (c), and PS (d) are automatically generated by the software, showing low BF and BV values within the lesion. [20]

Similarly, in a study of 17 patients, Zima et al. 2007 [7] demonstrated that elevated pretreatment values of BF and BV CTp parameters showed a significant correlation with response to induction chemotherapy evaluated endoscopically. They used BV values distribution as the predictor of response to induction chemotherapy in the development of the model as BV measurements were more tightly clustered in nonresponders with less overlap with responders than the distribution of BF in the same groups. They concluded that lower pretherapy levels of BV correlated with failed response to induction chemotherapy. With this information, they were able to develop a predictive model to potentially eliminate the need for induction therapy when deciding on an appropriate treatment regimen. (Figure 17).

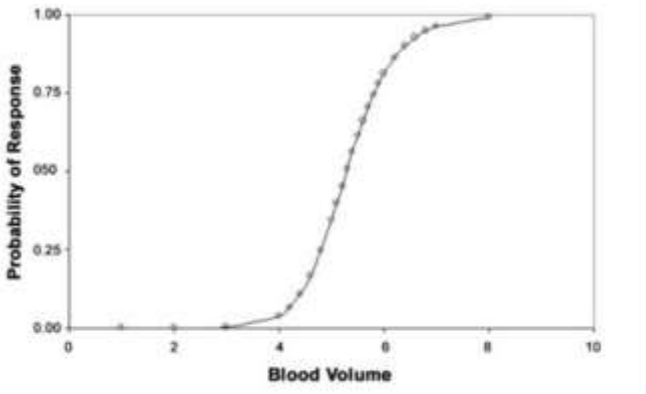


Figure 17. The probability of response to induction chemotherapy as a function of BV. [7]

Bisdas et al. 2009a [27] confirmed these results showing correlation between radiological response after induction chemotherapy and CTp parameters at baseline while just a weak correlation with pretreatment tumor volume was found. With these findings CTp perfusion parameters seemed to outperform the morphologic characteristics, being significantly different between responders and nonresponders with high BF, BV, and PS and low MTT correlated with a better tumor response, presumably reflecting better tumor oxygenation. The authors concluded their paper highlighting the role of CTp as a noninvasive, inexpensive, and widely accessible diagnostic tool, able to improve the choice of organ preservation treatment regimens in order to maximize the therapeutic efficacy [27]. Bisdas et al. 2009b [29] highlighted for first time the stronger (than tumor volume) significant predictive role of BF max values as well as the predictive role of PS mean values in HNC therapy options. These functional parameters were based on a new ROI analysis, using the maximum values, in assessing the outcome of the adjuvant chemoradiation after primary surgery, which could be helpful in selection of therapeutic options for individual patients.

Bisdas et al. 2010 [30] found that the BF, BF-BV mismatch and PS were predictive (P< 0.001) but BV and MTT held no significant predictive values for local tumor control. The patients with high perfusion had a longer local tumor control than the patients with hypoperfused tumors. In a study conducted by Pietsch et al. 2015 [32], they measured initially high CTP values (BF, BV) during staging of tumor tissue as a possible marker for high MVD and tumor oxygenation. Interestingly, those patients with recurrent disease had higher initial CTP-values as a possible marker for a more aggressive disease as compared to the recurrence- free patients. The study showed that by analyzing the pretherapeutic BV, a prediction of posttherapeutic local recurrence might be possible.

In a study done by Rana et al. 2015 [33], There was significant decrease in BF and BV and increase in MTT at 66 Gy among responders to CRT. This may be attributed to cytotoxic effect of radiotherapy to the vascular endothelial cells. The fluctuation of perfusion parameters during the course of therapy is due to hypoxia which may lead to decrease in perfusion and intratumoral inflammation that further lead to increase in BF and PS. The results showed that baseline BF was the only perfusion parameters that was significantly higher among responders as compared to non-responders to CRT. BF and a combination of high BF and low PS can be served as predictors for complete response.

In a small population study evaluating nasopharangeal cancer response to CRT using CTp measures, Tuntiyatorn et al. 2014 [34] found a positive correlation between initial BF and BV with tumor volume and a strongest positive correlation between higher pre-treatment permeability and degree of primary tumor volume reduction particularly among the responders. They postulated that PS was excellent parameter with high sensitivity and specificity to predict treatment response. Results from other works [8,11,21,37–46] studied application of CTp in oncology in different body parts are inconstant with what we reached about CTp prognostic role. The development of new blood vessels, an adaptive tumoral response to hypoxia, is an indirect marker that is depicted on perfusion CT images as an increase in tumor BF, BV, MTT, permeability, or a combination thereof [47]. As with CT perfusion, it is postulated that higher intratumoral MVD reflects increased oxygenation and subsequently can be used as a marker for increased sensitivity of tumors to radiation and/or chemotherapy. A positive correlation between BF and BV in HNSCC and intratumoral MVD had been demonstrated by others [48] (figure 18).

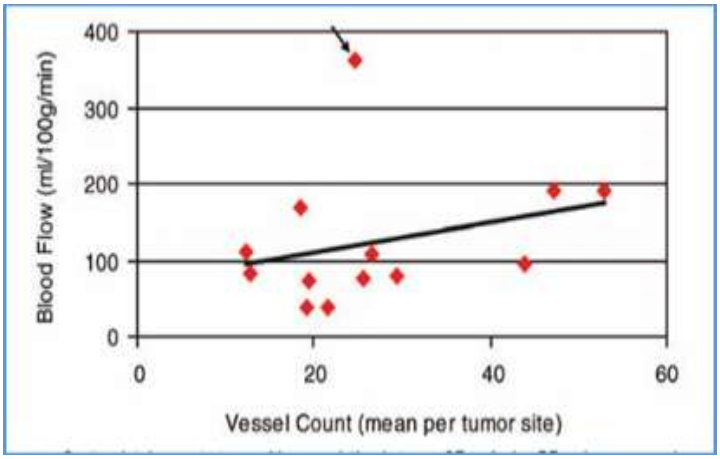


Figure 18: Scatterplot demonstrates positive correlation between CT perfusion BF (left), BV (right) and mean vessel count at HNSCC primary tumor sites. Among the 13 patients forming the study population, there was a single outlier (arrow). [48]

Although there was some sort of consensus about usefulness of CTp values in evaluation treatment response, we noticed some diverseness in results pooled from reviewed studies. Methodology heterogeneities among the clinical studies, such as initial presence of contrast agent, different time of scan initiation, and different acquisition durations as well as different treatment modalities and the different endpoints for local control could explain the diverse results [49,50]. The deconvolution analysis of perfusion images remains a robust technique, despite some limitations, and is the most feasible and reliable means for measuring the perfusion parameter both in the research and clinical realm. Moreover, perfusion CT is indeed more widely available and accessible, well tolerated in patients, and less time consuming [18][49]. The present systematic review had various limitations which are that of enrolled studies. Small size of the patient population, heterogeneity of the patient population, considering different end points of outcome and correlating the findings with short-term follow-up are main limitation that must be considered. Moreover, enrolling HNC in various stages and type is probably a confounding factor for the therapy results.

V. Conclusion

This meta-analysis or systematic review demonstrated the feasibility for routine clinical use of the perfusion CT using deconvolution analysis for the assessment of perfusion and permeability role in evaluating response to chemoradation in HNC of different stages. All the preliminary results of reviewed studies show that elevated CT perfusion parameters are statistically correlated to a better response to radiotherapy and chemotherapy and prove that tissue oxygenation may also influence the action of chemotherapy agents and enhance radiosensitivity. They highlighted BV and BF as the most significant CTp parameters as they may predict response to radio and chemotherapy and may help monitor both treatments. Although PS and MTT parameters are insufficiently predictive of the response in majority of studies, some papers highlighted their achievable effectiveness.

The obtained perfusion measurements were sufficient for differentiating neoplastic from normal tissue as well as responders from nonresponders. Hence, it is rationale to use baseline CTp parameters values as predictors of therapy response, locoregional control and disease recurrence. These findings have potential clinical applications regarding noninvasive treatment monitoring in patients with HNSCC treated with nonsurgical organ preservation therapy. In addition, CT perfusion does have the potential to monitor treatment response by enabling noninvasive assessment of alterations in tumor vasculation and serving as a surrogate marker for tumor oxygenation. Accurate assessment of tumor response could justify dose modulation or alternative treatment options if the functional parameters indicate non response among tumors treated with nonsurgical organ preservation therapy. However, prospective multi- institutional study of larger patient population and long term follow up is required to validate these results.

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