# USO DO PET-SCAN COMO PREDITOR DE EFICÁCIA PARA CONTROLE LOCOREGIONAL E SOBREVIDA EM CARCINOMA EPIDERMÓIDE DE CABEÇA E PESCOÇO

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**Área de concentração: Oncologia**

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# RESUMO

Nicolau UR. **Uso do PET-SCAN como preditor de eficácia para controle locoregional e sobrevida em carcinoma de cabeça e pescoço.** São Paulo; 2019. [Tese de Doutorado-Fundação Antônio Prudente].

Introdução: A avaliação da resposta à quimioterapia de indução (QI) com regimes triplos, incluindo taxane, cisplatina e 5 fluorouracil (TPF) em carcinoma de células escamosas de cabeça e pescoço localmente avançado (CECCPLA) é geralmente realizada após 2 ciclos de quimioterapia usando critérios morfológicos. Preocupações em relação ao perfil de toxicidade do TPF sugerem um benefício potencial de uma abordagem de avaliação de resposta precoce. Objetivo: o objetivo deste estudo é avaliar a utilidade de se avaliar precocemente a resposta tumoral por método funcional e morfológico com uso do PET-SCAN em pacientes portadores de CECCPLA tratados com QI seguido de radioteapia após o primeiro ciclo de QI. Métodos: Pacientes com CECCPLA que se submeteram ao QI com TPF foram avaliados prospectivamente. Os procedimentos de estadiamento incluíram imagem locorregional e de tórax, exame endoscópico e PET-SCAN. Pacientes foram avaliados para resposta tumoral após o segundo ciclo da QI e ao término do tratamento, conforme conduta estabelecida para a prática clínica. No dia 14 do primeiro ciclo, um segundo PET- SCAN foi realizado e os médicos e pacientes foram cegados para os seus resultados. Todos os pacientes assinaram consentimento para participação do estudo. Resultados: Entre fevereiro de 2010 e julho de 2013, 49 pacientes portadores de CECCPLA estádio III / IVA-B CECCPLA foram recrutados. Após um seguimento mediano de 44,3 meses, pacientes cujos achados de PET-SCAN não registraram aumento no Stardard Uptake Value (SUV) máximo dos linfonodos regionais apresentaram melhor sobrevida livre de recidiva (HR = 0,18; IC95% 0,056-0,585; p = 0,004) e sobrevida global (HR = 0,14, IC 95% 0,040-0,498; p = 0,002) e foram considerados respondedores.

Neste subgrupo, os pacientes que atingiram pelo menos 45% de redução no SUV máximo do tumor primário apresentaram melhor sobrevida livre de progressão tumoral (HR = 0,23, IC 95% 0,062-0,854; p = 0,028) e sobrevida global (HR = 0,11, IC 95% 0,013 -0,96; p = 0,046). Conclusão: Estes resultados sugerem um potencial papel da avaliação da resposta tumoral precoce com PET-SCAN em pacientes com CECCPLA submetidos a QI. Aumento no SUV máximo do linfonodo regional e diminuição insuficiente na captação do tumor primário predizem pior evolução clínca.

**Descritores**: Neoplasias de Cabeça e Pescoço. Quimioterapia de Indução. Radioterapia. Carcinoma de Células Escamosas. Papiloma Vírus Humano. Tomografia Computadorizada com Tomografia por Emissão de Pósitrons.

# SUMMARY

Nicolau UR. **[Use of PET-SCAN as a predictor of efficacy for locoregional control and survival in head and neck carcinoma].** Sao Paulo; 2019. [Tese Doutorado-Fundação Antônio Prudente].

Introduction: Evaluation of induction chemotherapy (IC) response with triplet taxane, cisplatin and 5 fluorouracil containing regimen (TPF) in locally advanced head and neck squamous cell carcinoma (LASCCHN) is usually performed after 2 cycles of chemotherapy using morphological criteria. Concerns regarding the TPF toxicity profile suggest a potential benefit of an early tumor response assessment approach. Objective: The objective of this study is to evaluate the usefulness of early evaluation of tumor response by functional and morphological method using PET-SCAN patients with LASCCHN treated with IC followed by radiotherapy after the first IC cycle. Methods: Patients with LASCCHN who underwent IC with TPF were prospectively evaluated. Staging procedures included standard primary neck tumor and chest imaging, endoscopic examination and PET-SCAN. Patients were evaluated for tumor response after the second cycle of IC and at the end of treatment, according to established practice guidelines. On day 14 of the first cycle, a second PET-SCAN was performed and physicians and patients were blinded to their exam findings. Results: Between February 2010 and July 2013, 49 patients staged AJCC III / IVA-B LASCCHN were recruited. After a median follow-up of 44.3 months, patients with no increase in the regional maximum lymph node SUV had better relapse-free survival (HR = 0.18, 95% CI 0.056-0.585, p = 0.004) and overall survival (HR = 0.14, 95% CI 0.040-0.498, p = 0.002) and were considered responders. Among cases considered responders, patients who achieved at least 45% reduction of SUV in the primary tumor presented improvement in progression-free (HR = 0.23, 95% CI 0.062-0.854, p = 0.028) and overall survival (HR = 0.11, 95% CI 0.013 -0.96, p = 0.046). All patients provided informed consent for study

participation. Conclusion: These results suggest an important role of the evaluation of the early response with PET-SCAN in patients with LASCCHN undergoing IC. Increase in the regional SUV maximum and insufficient decrease in primary tumor uptake predict worse clinical outcome.

**Key-words**: Head and Neck Neoplasms. Chemotherapy. Radiotherapy. Carcinoma, Squamous Cell. Papillomaviridae. Positron Emission Tomography Computed Tomography.

# LISTA DE SIGLAS E ABREVIATURAS

| | |
|---|---|
| **18FDG PET/CT** | 18 Fluorodesoxiglucose Positron Emission Tomography |
| **CECCP** | Carcinoma Espinocelular de Cabeça e Pescoço |
| **CECCPLA** | Carcinoma de células escamosas de cabeça e pescoço localmente avançado |
| **CO** | Carcinoma de Orofaringe |
| **EGOG** | Eastern Cooperative Oncologic Group |
| **HPV** | Papiloma Vírus Humano |
| **IMRT** | Radioterapia de Intensidade modulada |
| **LASCCHN** | Locally Advanced Head and Neck Squamous Cell Carcinoma |
| **mWHO** | Modified World Health Organization |
| **OMS** | Organização Mundial de Saúde |
| **PET-SCAN** | Positron Emission Tomography |
| **QI** | Quimioterapia de indução |
| **ReBEC** | Registro Brasileiro de Ensaios Clínicos |
| **RM** | Ressonância Nuclear Magnética |
| **SG** | Sobrevida Global |
| **SLP** | Sobrevida Livre de Progressão Tumoral |
| **SUV** | Standard Uptake Value |
| **TC** | Tomografias Computadorizadas |
| **TPF** | Taxane, Cisplatina e 5 fluorouracil |
| **WHO** | World Health Organization |

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# 1 INTRODUÇÃO

Existe um crescente interesse na utilização de avaliações por imagem morfo-metabólicas no manejo clínico de pacientes portadores de carcinoma espinocelular de cabeça e pescoço (CECCP), com destaque para o uso da Tomografia Computadorizada com Tomografia por emissão de pósitrons (18FDG PET/CT). Estudos publicados na última década demonstraram o potencial uso do 18.FDG PET/CT no manejo clínico destes pacientes pelo seu papel no estadiamento tumoral, investigação de sítio primário para pacientes portadores de disseminação linfonodal cervical por CECCP de sítio primário indeterminado, abordagem de linfonodos cervicais regionais após radioterapia associado a terapia citotóxica, seguimento clínico, e no planejamento da radioterapia (JOHANSEN et al. 2008; LONNEUX et al. 2010; DUPREZ et al. 2011; MEHANNA et al. 2016).

Em estudo clínico que avaliou 233 pacientes recém diagnosticados CECCP, demonstrou-se que a complementação do estadiamento com uso de 18 FDG PET/CT foi capaz de levar a alterações de estadiamento que acarretaram mudança no planejamento terapêutico em 13,7%% dos casos (LONNEUX et al. 2010).

Em 2008, JOHANSEN et al. conduziram estudo que avaliou 60 pacientes diagnosticados com CECCP com disseminação linfonodal cervical de sítio primário desconhecido, em que se demonstrou a capacidade de se elucidar o sítio primário da neoplasia em 29% dos casos quando 18.FDG

PET/CT foi incluído na investigação destes pacientes, levando a mudança no planejamento terapêutico de 25% dos casos, e estabelecendo o papel do 18. FDG PET/CT na avaliação destes pacientes.

O uso do método morfo-metabólico 18 FDG PET/CT após radioterapia com intuito curativo foi avaliado em estudo publicado em 2016, onde 564 pacientes foram randomizados para avaliação da segurança de se poupar do esvaziamento linfonodal cervical planejado após radio quimioterapia pacientes portadores de CECCP localmente avançado, com volume tumoral linfonodal “N2/N3” com resposta linfonodal completa por avaliação clínico radiológica convencional, e confirmada em avaliação por 18.FDG PET/CT 12 semanas após o término da radioterapia . Neste estudo demonstrou-se a segurança em se realizar seguimento clínico em pacientes que apresentaram resposta tumoral completa confirmada pelo método morfo-metabólico, denotando, portanto o alto valor preditivo negativo do 18.FDG PET/CT neste cenário (MEHANNA et al. 2016).

Devido à crescente demanda por se individualizar terapias, discute-se ainda o potencial uso de avaliações de resposta tumoral morfo-metabólicas precocemente no curso de terapias anti-neoplásicas visando melhor seleção de pacientes portadores de tumores responsivos à terapia em curso, evitando-se toxicidades e efeitos adversos de tratamentos precocemente, viabilizando, portanto selecionar pacientes a prosseguirem no tratamento em curso ou mudança de estratégia terapêutica durante suas etapas iniciais (DE BREE et al. 2017).

O uso de terapias não cirúrgicas em pacientes portadores de CECCP localmente avançado se dá usualmente pela associação de terapia radiossensbilizante citotóxica baseada em compostos de platina associados à radioterapia no modo concomitante. Estudos realizados e publicados durante a década de 90 do século XX e dados de meta-análises estabeleceram o uso de associação da terapia citotóxica baseada em platina associado à radioterapia, preferencialmente no modo concomitante, como terapia preferencial na abordagem inicial não-cirúrgica de pacientes portadores de CECCP localmente avançado, como parte de estratégia preservadora de órgãos e também na doença localmente avançada considerada irressecável (JEREMIC et al. 2000; PIGNON et al. 2000; FORASTIERE et al. 2003; ADELSTEIN et al. 2003; DENIS et al. 2004).

A demonstração em estudos randomizados recentes de que novas combinações triplas (com associação de taxanes) são superiores aos antigos regimes duplos (platina + 5-Fluorouracil) em quimioterapia de indução tornaram os regimes de quimioterapia de indução seguidos de radioterapia uma opção terapêutica neste cenário. Considerando-se o conceito de que sensibilidade tumoral a quimioterapia de indução prediz radio-sensibilidade tumoral e evolução terapêutica, pacientes são rotineiramente avaliados inicialmente para resposta tumoral no decurso da terapia proposta após o segundo ciclo de quimioterapia de indução (POSNER et al. 2007; VERMORKEN et al. 2007; POINTREAU et al. 2009).

Devido elevadas taxas de toxicidade, com mais de 70 % de pacientes apresentando toxicidades grau 3 ou maior, discute-se o benefício em se

avaliar precocemente a resposta terapêutica no curso do tratamento de pacientes portadores de CECCP localmente avançado, com ferramentas que se mostrem capazes de melhor selecionar pacientes sensíveis à terapia sistêmica e terapia radioterapia.

# 2 OBJETIVO

O objetivo deste estudo é avaliar a correlação da variação precoce de SUV máximo na topografia do tumor primário avaliado com 18-FDG PET /CT com a eficácia do tratamento de pacientes tratados com Quimioterapia de indução seguido de radioterapia para o tratamento de CECP Localmente Avançado, nos sítios primários de orofaringe, laringe, hipofaringe e cavidade oral.

# 3 METODOLOGIA

## 3.1 DESENHO DO ESTUDO

Este é um estudo prospectivo, de braço único e não controlado, realizado em centro único. O estudo foi revisado e aprovado pelo Comitê de Ética em Pesquisa da Fundação Antonio Prudente/A.C.Camargo Cancer Center em 10 de novembro de 2009 sob o registro 1288/09. (Anexo 1). Relatórios semestrais dirigidos ao Comitê de Pesquisas do A.C.Camargo Cancer Center foi realizado durante o período de recrutamento dos pacientes. O ensaio está registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC) pelo número RBR-9WWSTD. Termo de Consentimento informado por escrito foi obtido de todos os pacientes. Todos os procedimentos relacionados ao estudo foram realizados após assinatura do Termo de Consentimento. Todos os pacientes que assinaram o Termo de Consentimento informado para a participação no estudo foram analisados no presente relatório (Apêndice 1).

## 3.2 POPULAÇÃO DO ESTUDO

Pacientes portadores de CECCP localmente avançado foram incluídos entre fevereiro de 2010 e julho de 2013, com uma mediana de seguimento de 44,3 meses na época da análise final. Os critérios de

elegibilidade dos pacientes para este estudo incluíram: um diagnóstico histologicamente confirmado de estágio III não tratado ou IVA / B, de acordo ao sistema de estadiamento do *AJCC Cancer Staging Manual* (7ª edição): tumores oriundos da orofaringe, hipofaringe, laringe ou cavidade oral; uma idade mínima de 18 anos; status de desempenho, ECOG 0-1; e ausência de co-morbidades principais ou disfunções orgânicas impeditivas.

## 3.3 PROTOCOLOS DE IMAGEM

Todos exames de imagem foram realizados no mesmo equipamento e duas radiologistas experientes revisaram todas as imagens de tomografia computadorizada e ressonância magnética. As tomografias computadorizadas (TC) foram realizadas com um scanner de TC de fileira com múltiplos detectores de 16 secções, TC de cabeça e pescoço foi realizada após administração de 80 a 120 mL de contraste não iônico. Exames de ressonância magnética (RM) foram realizados em aparelhos de 1,5 T. O protocolo de RM incluiu imagens axiais ponderadas em T1 e T2, imagens saturadas de gordura ponderadas em T2 coronal e imagens em T1 após administração intravenosa de contraste paramagnético à base de gadolínio (10 ml de gadoversetamida, Optimark® Mallinckrodt). Imagens de PET / CT de corpo inteiro com 18F-FDG foram realizadas 60 minutos após a injeção intravenosa de 0,154 mCi / Kg de 18F-FDG (IPEN-CNEN). Pacientes com níveis normais de glicose no sangue foram injetados em repouso e após pelo menos 4 horas de jejum. Ambos os protocolos de tomografia

computadorizada de baixa dose e PET dedicado, a partir da cabeça até a coxa proximal, foram adquiridos em PET / CT de 64 canais. Especialistas em medicina nuclear com 15 e 25 anos de experiência analisaram imagens e dados de SUV em concordância.

## 3.4 DIAGNÓSTICO, ESTADIAMENTO, PLANO DE TRATAMENTO E AVALIAÇÃO DE RESPOSTA

Pacientes com tumores em estádio III-IVA/B foram avaliados prospectivamente e submetidos a Quimioterapia de Indução (QI) com Taxane, Cisplatina e 5 Fluouracil seguido de Radioterapia. Os procedimentos de estadiamento incluíram exame físico e endoscópico, e TC ou RM de tumor primário, pescoço e tórax. Um exame PET / CT de base foi realizado para todos os pacientes, e o Standard Uptake Value (SUV) máximo pré-tratamento de tumores primários e metástases de linfonodos regionais cervicais foram registrados. Vale ressaltar que, para os pacientes portadores de carcinoma de orofaringe (CO), o teste para detecção do Papiloma Vírus Humano (HPV) foi implementado em nosso centro de rotineiramente a partir de 2013. Desta forma, os pacientes com CO com amostras de tecido disponíveis foram testados para HPV por coloração de p16 ou genotipagem de HPV de alto risco.

## 3.5 QUIMIOTERAPIA DE INDUÇÃO E TERAPIA RADIOSSENSIBILIZANTE

Os pacientes foram tratados com 3 a 4 ciclos de QI com um taxano (paclitaxel, 175mg / m2 ou docetaxel, 75mg / m2) combinado com 75-100 mg / m2 de cisplatina no dia 1 e infusão contínua de 750 mg / m2 5-fluorouracil diariamente por 5 dias. Os agentes radiossensibilizadores propostos para uso concomitante a radioterapia incluíram carboplatina semanal (área sob a curva, 1,5) e 100 mg / m2 de cisplatina a cada 3 semanas.

## 3.6 RADIOTERAPIA

Radioterapia de Intensidade modulada (IMRT) ou terapias conformacionais tridimensionais foram permitidas para a entrada no estudo. Os tratamentos foram realizados em aceleradores lineares com fótons de 6 MV. As doses máximas para o volume tumoral bruto (doença macroscópica) foram de 66 a 70 Gy, durante 6 a 8 semanas.

## 3.7 AVALIAÇÃO DA RESPOSTA AO TUMOR, PROCEDIMENTOS EXPERIMENTAIS E ACOMPANHAMENTO DE PACIENTES

Todos os casos foram avaliados de acordo com os critérios padrões da Organização Mundial de Saúde (WHO) para avaliação da doença. Após o

segundo ciclo, a resposta do tumor foi avaliada pelo médico assistente, através de exame físico e endoscópico, e TC ou ressonância magnética do tumor / pescoço. Pacientes com redução de dimensão tumoral, de acordo com os critérios da WHO ou mWHO, foram selecionados para um novo ciclo de quimioterapia de Indução seguido de radioterapia.

## 3.8 PROCEDIMENTOS DE GERAÇÃO DE IMAGENS EXPERIMENTAIS

No décimo quarto dia do primeiro ciclo de QI (D14-C1-QI), um segundo 18-FDG PET / CT foi realizado e os SUVs máximos no tumor primário e na metástase regional dos linfonodos cervicais foram registrados. As variações de SUV máximo no tumor primário e nas cadeias linfonodais regionais obtidas pela análise comparativa dos 02 exames de 18.FDG PET/CT não eram acessadas pelo médico assistente ou pelos pacientes tratados. Todos os pacientes foram avaliados e conduzidos clinicamente de acordo com critério morfológico convencional de avaliação de resposta tumoral após o segundo ciclo de QI, em que pacientes portadores de tumores responsivos à QI eram submetidos a radioterapia associada a terapia radiosensibilizante concomitante.

## 3.9 ACOMPANHAMENTO DE PACIENTES

Após o tratamento, os pacientes foram inicialmente avaliados por exame físico e monitoração laboratorial de toxicidade e resposta tumoral, e depois mensalmente. A TC ou a RM foram realizadas a cada 2 meses após o término da radioterapia. Visitas de acompanhamento para avaliações de eficácia e segurança foram programadas a cada 1 ou 2 meses durante o primeiro ano, a cada 2 ou 3 meses durante o segundo e terceiro ano e a cada 6 meses a partir de então. Após o término do tratamento, exames de imagem de cabeça e pescoço e de tórax foram realizados a cada 4 meses no primeiro ano, a cada 4-6 meses no segundo ano e anualmente. Esforços foram feitos para confirmar recorrência tumoral patológica e doença progressiva nos casos clinicamente exigidos, de acordo com a prática clínica institucional atual.

## 3.10 ANÁLISES ESTATÍSTICA

As características dos pacientes são expressas como frequências absolutas e relativas para variáveis qualitativas, e como mediana e intervalo para variáveis quantitativas. O desfecho primário do estudo foi sobrevida livre de progressão. Para os pacientes com qualquer redução dos gânglios linfáticos do pescoço, SUV máximo e sem progressão da doença à distância, comparamos a Sobrevida Livre de Progressão (SLP) de dois grupos de pacientes de acordo com a extensão da redução máxima do SUV

do tumor primário após o primeiro ciclo de QI. Os dois grupos foram gerados utilizando um ponto de corte derivado post-hoc da redução máxima do SUV do tumor primário de acordo com a estatística de log-rank máxima padronizada. A estatística de log-rank maximamente selecionada para pontos de corte entre percentis de 5% e 95% de variáveis contínuas (variação no SUV máximo do tumor primário) foi considerada. Como desfecho secundário, avaliamos a diferença na sobrevida global de acordo com a redução máxima do SUV no tumor primário após o primeiro ciclo de QI. Também avaliamos Sobrevida Livre de Progressão (SLP) e Sobrevida Global (SG) de acordo com os critérios de resposta da Organização Mundial da Saúde (WHO) e sua versão modificada mWHO. Além disso, uma análise de subgrupo foi realizada em pacientes com CO. O estimador de Kaplan-Meier foi usado para análise de sobrevivência, e testes log-rank foram aplicados para comparar as distribuições de sobrevivência entre os grupos. O modelo de riscos proporcional de Cox foi usado para descrever a relação entre variáveis de ponto de tempo e covariáveis. A hipótese de proporcionalidade foi avaliada usando o teste de resíduos de Schoenfeld. Em todos os casos, havia evidências de que as covariáveis tiveram um efeito constante ao longo do tempo. Considerando o tamanho da amostra relativamente pequeno, o corte de redução máxima do SUV do tumor primário, derivado do máximo da estatística log-rank padronizada, foi submetido à amostragem não paramétrica de 10.000 bootstrap com substituição para validação interna, aplicada à SLP e SG.

# 4 ARTIGO

Nicolau UR, de Jesus VHF, Lima ENP, Alves MS, de Oliveira TB, Andrade LB, Silva VS, Bes PC, de Paiva TF Jr, Calsavara VF, Guimarães APG, Cezana L, Barbosa PNVP, Porto GCLM, Pellizzon ACA, de Carvalho GB, Kowalski LP. Early metabolic 18F-FDG PET/CT response of locally advanced squamous-cell carcinoma of head and neck to induction chemotherapy: a prospective pilot study. **PLoS One** 2018 Aug 16; 13(8):e0200823. doi: 10.1371/journal.pone.0200823. eCollection 2018. PMID: 30114190

PLOS ONE

RESEARCH ARTICLE

# Early metabolic 18F-FDG PET/CT response of locally advanced squamous-cell carcinoma of head and neck to induction chemotherapy: A prospective pilot study

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## Abstract

### Objective

The objective of this study was to assess the clinical value of 18-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) after the first cycle of induction chemotherapy (IC) in locally advanced squamous cell carcinoma of the head and neck (LASCCHN).

### Methods and findings

A prospective, single-arm, single center study was performed, with patients enrolled between February 2010 and July 2013.Patients (n = 49) with stage III/IVA–B LASCCHN who underwent IC with taxanes, cisplatin, and fluorouracil were recruited. Staging procedures included loco-regional and chest imaging, endoscopic examination, and PET/CT scan. On day 14 of the first cycle, a second PET/CT scan was performed. Patients with no early increase in regional lymph node maximum $^{18}$F-FDG standard uptake value (SUV), detected using $^{18}$F-FDG PET/CT after first IC had better progression-free survival (hazard ratio (HR) = 0.18, 95%, confidence interval (CI) 0.056–0.585; p = 0.004) and overall survival (HR = 0.14, 95% CI 0.040–0.498; p = 0.002), and were considered responders. In this subgroup, patients who achieved a reduction of $\geq$ 45% maximum primary tumor SUV experienced improved progression-free (HR = 0.23, 95% CI 0.062–0.854; p = 0.028) and overall (HR = 0.11, 95% CI 0.013–0.96; p = 0.046) survival.

## Conclusions

These results suggest a potential role for early response evaluation with PET/CT examination in patients with LASCCHN undergoing IC. Increased regional lymph node maximum SUV and insufficient decrease in primary tumor uptake predict poorer outcomes.


## Introduction

Phase III trials and meta-analyses published during the 1990s established radiotherapy combined with chemotherapy (generally administered concurrently) as standard treatment for patients demanding organ-preservation or harboring unresectable locally advanced squamous-cell carcinoma of the head and neck (LASCCHN) [1–8].

In the last decade, randomized trials comparing induction chemotherapy (IC) regimens where taxanes were added to cisplatin and fluorouracil (TPF) to the previous standard, cisplatin plus fluorouracil (PF), regimen demonstrated improved outcomes favoring taxane-containing triplet regimens and led to the introduction of IC with triplet regimens followed by radiotherapy as a treatment option for patients with LASCCHN. However, despite their greater efficacy, grade 3 or higher toxicity, occurring in more than 70% of patients, has limited the use of triplet regimens [9–12].

Clinical, endoscopic, and radiological tumor response evaluation to IC-CT RT for LASCCHN is usually performed after 2-IC cycles, based on the anatomic World Health Organization (WHO) or modified WHO (mWHO) criteria, in which a partial response requires a bi-dimensional decrease in the target lesion of 50% and 25%, respectively, and neither increase in the regional neck lymph node lesions, nor evidence of distant metastasis. Patients whose primary tumors or regional lymph nodes experience an enlargement higher than 25% in their bi-dimensional diameters during IC experience disease progression according to the WHO criteria and they are usually treated with salvage surgery. Accordingly, patients developing distant metastasis are considered as patients harboring non-responsive tumors and are often treated with palliative systemic therapy. Patients with primary tumors that exhibit at least a partial response, according to computed tomography (CT) or magnetic resonance imaging (MRI) evaluation, are usually treated using sequential radiotherapy with concurrent chemotherapy or biotherapy (CBRT) [9–10,13–15].

Concerns regarding the toxicity profile of triple IC regimens suggest that early response evaluation could identify patients harboring non-responsive tumors, who could be spared from toxicity by prompt initiation of an alternative treatment [16–17]. Moreover, the identification of a subgroup of patients with HPV-related oropharyngeal squamous-cell carcinoma (OPSCC) with favorable prognosis raised the prospect of safe de-intensification protocols for some patients, according to early tumor response evaluation [18–23].

Positron emission tomography/Computed tomography (PET/CT) using the glucose analog fluorodeoxyglucose F-18 ($^{18}$F-FDG) is employed in head and neck squamous-cell carcinoma (HNSCC) for staging, management of unknown primary tumor, post-radiotherapy response evaluation, and patient surveillance [24–32]. $^{18}$F-FDG PET/CT has demonstrated ability to identify groups of patients with other malignant diseases with better clinical outcomes early in the course of treatment [33–36]. Therefore, we conducted a prospective trial to test the hypothesis that an early decrease in $^{18}$F-FDG uptake, measured by standard uptake value (SUV) change, detected using $^{18}$F-FDG PET/CT after the first cycle of IC could identify patients with improved clinical outcomes. The aim of the trial was to examine the relationship between

changes in primary tumor maximal SUV from baseline to post-cycle 1 $^{18}$F-FDG PET/CT with progression-free survival (PFS).

Furthermore, we tested whether early functional $^{18}$F-FDG PET/CT imaging could replace the standard post-second-cycle anatomical WHO and mWHO evaluation for patients treated for LASCCHN using IC followed by CBRT.

## Materials and methods

### Study design and compliance with ethical standards

The study was a prospective, single-arm, single center trial; it was reviewed and approved by the Antonio Prudente Foundation /AC Camargo Cancer Center Research Board on November 10, 2009 under registration number 1288/09. An every 6 months report for AC Camargo Cancer Center Research Board was performed during enrollment patients period. The trial was designed and approved in 2009, and followed all the regulatory Brazilian law demands for prospective trial registering requirements involving human subject research at that period. The trial is registered at the Brazilian Clinical Trials Registry (ReBEC) RBR-9WWSTD. The trial was registered in the ReBEC after opening the period for patients enrollment because the Brazilian system for clinical trials Registry started its activities on 2010. Written informed consent was obtained from all patients. All patients who signed the informed consent for the trial participation are analyzed in the present report. The authors confirm that all on going and related trials for this intervention are registered. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee, and with the 1964 Helsinki declaration and its later amendments.

### Population

Between February 2010 and July 2013 eligible patients were enrolled, with a median follow-period of 44.3 months at the time of this analysis. Patient eligibility criteria for this study included: a histologically confirmed diagnosis of untreated stage III or IVA/B HNSCC, according to the AJCC staging system (6th edition); tumors arising from the oropharynx, hypopharynx, larynx, or oral cavity; a minimum age of 18 years; performance status, ECOG 0–1; and absence of impeditive major co-morbidities or organ dysfunctions.

### Imaging protocols

All the imaging exams were performed in the same technical equipment.

CT scans were performed using a 16-section multidetector row CT scanner (Philips Brilliance Big Bore, Philips Healthcare, Cleveland, OH). Head and neck CT was performed after administration of 80–120 mL of a nonionic contrast (Optiray 320; Mallinckrodt). MRI examinations were performed at 1.5 T MR scan (SignaHDxT system, GE Medical Systems, Milwaukee, WI). MRI protocol included axial T1-and T2-weighted images, coronal T2-weighted fat saturated images and T1-weighted images after intravenous administration of gadolinium-based paramagnetic contrast agent (10 ml of gadoversetamide, Optimark® Mallinckrodt). Two experienced medical radiologists reviewed all CT and MRI images.

Whole body $^{18}$F-FDG PET/CT imaging was performed 60 minutes after intravenous injection of 0.154 mCi/Kg of $^{18}$F-FDG (IPEN-CNEN). Patients with normal blood glucose levels were injected at rest and after at least 4 hours of fasting. Both low dose CT and dedicated PET imaging protocols, starting from the head to the proximal thigh, were acquired in a 64 channel PET/CT (Gemini TOF, Philips Medical Systems). Nuclear medicine specialists with 15 and 25 years of experience reviewed images and SUV data in concordance.

## Tumor diagnosis, staging, treatment plan, and response evaluation

Patients with stage III–IVB LASCCHN were prospectively evaluated and underwent IC with TPF followed by CBRT. Staging procedures included physical and endoscopic examination, and CT or MRI of primary tumor, neck, and chest. A baseline PET/CT examination was performed for all patients, and the pre-treatment maximal SUV of primary tumors and regional neck lymph node metastases were recorded. It is noteworthy to point that in the mean time of development of this study a policy of routine HPV testing in primary OPSCC was implemented in our center. In this way, patients with OPSCC with available tissue samples were tested for HPV by p16 staining or high-risk HPV genotyping [23].

### Induction chemotherapy and radiosensitizing therapy

Patients were treated with 3–4 cycles of IC with a taxane (paclitaxel, 175mg/$m^2$or docetaxel, 75mg/$m^2$) combined with 75–100 mg/$m^2$ of cisplatin on day 1, and continuous infusion of 750 mg/$m^2$5-fluorouracil daily for 5 days. Radiosensitizers included weekly carboplatin (area under the curve, 1.5), and 100 mg/$m^2$cisplatin every 3 weeks.

### Radiotherapy

Intensity modulated radiotherapy (IMRT) or 3-dimensional conformal therapies were allowed for study entry. Treatments were performed in linear accelerators with 6 MV photons. Maximum doses for gross tumor volume (macroscopic disease) were 66–70 Gy, over 6–8 weeks.

### Tumor response evaluation, experimental procedures and patients follow-up

All cases were assessed according to standard WHO or mWHO criteria for disease evaluation. After the second cycle, tumor response was assessed by the treating physician, using physical and endoscopic examination, and primary tumor/neck CT or MRI. Patients with at least partial tumor shrinkage, according to WHO or mWHO criteria, were selected for a further cycle of IC followed by CBRT.

### Experimental imaging procedures

On the fourteenth day of the first IC cycle (D14-C1-IC), a second PET/CT was performed and the maximum SUVs in the primary tumor and regional neck lymph node metastasis recorded. Treating physicians and patients were blinded to these findings.

### Patients follow-up

After treatment, patients were initially evaluated by physical examination and laboratory monitoring for toxicity and tumor response, and then monthly. CT or MRI was performed within 2 months after the end of radiotherapy. Follow-up visits for efficacy and safety assessments were scheduled every 1–2 months during the first year, every 2–3 months during the second and third years, and every 6 months thereafter. After treatment completion, head and neck, and chest imaging examinations were performed every 4 months in the first year, every 4–6 months in the second year, and yearly afterwards. Efforts were made to confirm pathological tumor-recurrence and progressive disease in cases if clinically demanded, according to current institutional clinical practice.

### Statistical analyses

Patient characteristics are expressed as absolute and relative frequencies for qualitative variables, and as median and range for quantitative variables. The primary outcome of the study was progression-free survival. For patients with any reduction of neck lymph nodes'maximum SUV and no distant disease progression, we compared PFS of two group of patients according to the extent of primary tumor maximal SUV reduction following the first cycle of IC. The two groups were generated using a post-hoc derived cutoff of primary tumor maximal SUV reduction according to maximum standardized log-rank statistics [37]. The maximally selected log-rank statistics for cut-points between 5% and 95% percentiles of continuous variables (variation in primary tumor maximum SUV) were considered. As secondary outcome, we assessed the difference in overall survival according to primary tumor maximum SUV reduction following the first cycle of IC. We also evaluated PFS and OS according to WHO and mWHO response criteria. Moreover, a sub-group analysis was performed in OPSCC patients. The Kaplan-Meier estimator was used for survival analysis, and log-rank tests were applied to compare survival distributions between groups. The Cox proportional hazards model was used to describe the relationship between time-point variables and covariates [38]. Proportionality assumption was evaluated using the Schoenfeld residuals test [39–40]. In all cases, there was evidence that covariates had a constant effect over time. Considering the relatively small sample size, the primary tumor maximum SUV reduction cut-off, derived from the maximum of the standardized log-rank statistic, was subjected to non-parametric 10,000 bootstrap sampling with replacement for internal validation, applied to PFS and OS. All statistical analysis were performed using either the R statistical package or SPSS v21.0 software.

### Protocol deviations

One patient has performed the baseline PET/CT in a different equipment and was originally evaluated by an external nuclear medicine specialist due to an initial diagnosis investigation initiated in other hospital, and it was not performed in the pretreatment period in our hospital as demanded by protocol. This PET/CT imaging was available for evaluation of our nuclear medicine specialist evaluation at the time of the performance the post-cycle 1 IC experimental PET/CT. Two patients did not perform the D14 cycle 1 IC PET/CT and were not be included in this analysis for the reasons described in the results section. One patient performed the planned D14 cycle 1 IC PET/CT at the day 25 cycle 1 IC due to a upper aerodigestive tract infection that led to postpone the second IC cycle. The experimental post-cycle 1 PET/CT of this patient was performed before the cycle 2, after clinical recovery from infection. Seven patients underwent alternative post-TPF IC concurrent radiosensitizing therapy in accordance with assistant physician choice, which included weekly (instead of every 3 week) cisplatin for 3 patients, weekly cetuximab (at usual cetuximab loading dose 400mg/m2 followed by 250mg/m2 weekly infusion) for 3 patients, and exclusive radiotherapy for 1 patient.

## Results

Forty-nine consecutive patients diagnosed with LASCCHN were enrolled in this study. Table 1 shows the demographic and clinical characteristics of the patient population. The majority of patients were male, and smokers or former smokers. The most frequent primary tumor site was oropharynx, and tumors were often HPV-related. HPV status was determined in 26 (63%) of the 41 OPSCC patients. Forty patients presented with stage IV disease (Table 1 and S1 Table).

**Table 1. Demographic and clinical characteristics of the study population.**

| Characteristic | Patients (49) N (%) |
|---|---|
| Sex | |
| Male | 44 (90) |
| Female | 5 (10) |
| Age (years) | |
| Median (range) | 55 (39–74) |
| <50 | 13 (27) |
| 50–59 | 24 (49) |
| 60–69 | 10 (20) |
| ≥70 | 2 (4) |
| Smoking history | |
| Never | 14 (29) |
| Former | 15 (31) |
| Current | 20 (41) |
| Tumor site | |
| Oropharynx | 41 (84) |
| Larynx | 4 (8) |
| Hypopharynx | 4 (8) |
| Staging | |
| III | 9 (18) |
| IVA | 30 (61) |
| IVB | 10 (20) |
| Tumor staging | |
| T1–2 | 16 (33) |
| T3 | 22 (45) |
| T4 | 10 (20) |
| Tx | 1 (2) |
| Lymph Node staging | |
| N0–1 | 11 (22) |
| N2 | 31 (63) |
| N3 | 7 (14) |
| HPV status (oropharynx only) | |
| Positive | 19 (46) |
| Negative | 7 (17) |
| Unknown | 15 (37) |

Demographic and clinicopathological characteristics of the entire patient population (N = 49).
Staging followed AJCC recommendations (6th edition).

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Most patients received three cycles of IC, and docetaxel was the most frequently employed taxane. IMRT and concurrent carboplatin were the most frequently administered treatments (S2 Table).

## Assessments and outcomes

Two patients were not included in the primary outcome analysis because they were unable to undergo early(D14-C1-IC) $^{18}$F-FDG PET/CT examination because of post-cycle 1 grade 4 hyponatremia (1 patient), and synchronous colorectal cancer diagnosed by the baseline PET/

CT, demanding an immediate colonic resection, with subsequent IC followed by CBRT for LASCCHN treatment (1 patient). Both patients were alive and disease free at the time of this analysis.

Among the remaining 47 patients, 83% and 92% had morphologically responsive tumors, according to standard WHO and mWHO criteria, respectively. Patients whose tumors achieved at least partial response according to mWHO criteria received a third cycle of IC followed by CBRT. On D14-C1-IC PET/CT, nine patients showed SUV elevation in lymph nodes (six patients), primary tumors (two patients), or both primary tumor and lymph nodes (one patient). Hence, 40 (85%) patients demonstrated a decrease in lymph node SUV, and were considered to have metabolically responsive tumors. Table 2 illustrates individual patient responses according to PET/CT (change in primary tumor and regional lymph node maximum SUV), WHO, and mWHO criteria during IC. The Fig 1 describes the entire population consort flowchart. In Fig 2, we report two patients harboring responsive and non-responsive tumors according to D14 cycle 1 IC PET/CT evaluation, respectively.

After a median follow-up of 44.3 months (range, 2.0–70.6 months), 16 patients experienced progressive disease. There were 12 loco-regional, three distant, and one simultaneous loco-regional and distant progression of disease. Median PFS was not reached, and 3-year PFS was 69%. Ten patients died; all deaths were cancer-related. Median OS was not reached, and 3-year OS was 75%. Median follow-up was 41.6 months for surviving patients (range, 9.5–70.6 months).

Patients with responsive tumors experienced higher PFS than patients with non-responsive tumors according to morphological WHO criteria (log-rank $p < 0.001$), and there was a trend toward improved PFS favoring patients harboring responsive tumors by mWHO criteria (log-rank $p = 0.077$). These results were not translated into increased OS of responders, according to either criteria (log-rank $p = 0.74$ and 0.331 for WHO and mWHO, respectively).

Conversely, the 40 patients presenting with D14-C1-IC $^{18}$F-FDG PET/CT responsive tumors exhibited superior PFS (HR = 0.18, 95% CI 0.056–0.585; $p = 0.004$) and OS (HR = 0.14, 95% CI 0.040–0.498; $p = 0.002$) than those with non-responsive tumors (Fig 3). Moreover, among these 40 patients, the extent of decrease in SUV in primary tumors correlated with clinical outcome. According to the maximum of the standardized log-rank statistical analysis, patients whose primary tumors showed an SUV decrease of $\geq$45% from baseline on D14-C1-IC PET/CT exhibited higher PFS (HR = 0.23, 95% CI 0.062–0.854; $p = 0.028$) and OS (HR = 0.11, 95% CI 0.013–0.96; $p = 0.046$) (Fig 4). A post-hoc study power analysis performed using the PFS HR and a two-tailed alpha of 0.05 determined a statistical power of 0.64 (Beta = 0.36) to detect a meaningful difference in PFS according to primary tumor maximum SUV reduction. Bootstrap analysis confirmed these findings for both outcome measures.

Patients that did not achieve $\geq$45% decrease in primary tumor SUV and those who experienced an increase in neck SUV, had unfavorable outcomes (PFS and OS) compared with those that had a $\geq$ 45% reduction in primary tumor SUV associated with any reduction in neck SUV (Fig 5).

## Clinical outcomes of OPSCC patients according to HPV status

Among 39 primary OPSCC patients, 25 (64%) had their tumors tested for HPV. Patients with HPV-positive tumors experienced higher response rates during IC according to both mWHO criteria (100% vs. 86%; $p = 0.28$) and evaluation of neck lymph node SUV reduction on D14-C1-IC $^{18}$F-FDG PET/CT (100% vs. 57%; $p = 0.015$). Patients with HPV-negative tumors had inferior PFS (HR = 4.09, 95% CI 0.818–20.50; $p = 0.086$), and OS (HR = 9.97, 95% CI 1.03–96.64; $p = 0.047$). Patients with HPV-positive tumors considered metabolically

Table 2. Response to induction chemotherapy according to PET/CT.

| Patient no. | Site | Clinical Staging | $^{18}$F-FDG (max SUV)–T | | | $^{18}$F-FDG (max SUV)—N | | | Response (WHO) | Response (mWHO) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | Day 14 | Change (%) | Baseline | Day 14 | Change (%) | | |
| 1 | oropharynx | IVA | 7.21 | 6.34 | -13 | 4.3 | 3.4 | -21 | yes | yes |
| 2 | oropharynx | IVA | 16.07 | 6.79 | -58 | 7.6 | 4.88 | -36 | no | no |
| 3 | oropharynx | IVA | 3.32 | 2.83 | -15 | 7.3 | 4.08 | -44 | yes | yes |
| 4 | oropharynx | IVA | 7 | 4.3 | -39 | 4.55 | 2.22 | -51 | no | no |
| 5 | hypopharynx | IVB | 13.7 | 6.43 | -53 | 5.56 | 5.81 | 4 | no | yes |
| 6 | oropharynx | IVA | 12.9 | 10.4 | -19 | 6.5 | 3.47 | -47 | yes | yes |
| 7 | Larynx | III | 9.97 | 4.76 | -53 | 0 | 0 | 0 | yes | yes |
| 8 | oropharynx | III | 6.52 | 4.91 | -25 | 0 | 0 | 0 | yes | yes |
| 9 | oropharynx | IVB | 6.95 | 5.07 | -27 | 4.14 | 3.47 | -16 | yes | yes |
| 10 | oropharynx | IVA | 9.19 | 5 | -46 | 9.29 | 5.8 | -38 | yes | yes |
| 11 | oropharynx | III | 12.27 | 4.9 | -60 | 6.11 | 3.1 | -49 | yes | yes |
| 12 | oropharynx | IVA | 14 | 5.9 | -58 | 7.5 | 0 | -100 | yes | yes |
| 13 | hypopharynx | IVA | 10.1 | 11 | 9 | 8.4 | 8.3 | -1 | yes | yes |
| 14 | hypopharynx | IVA | 12.8 | 5.5 | -57 | 5.2 | 3.6 | -31 | yes | yes |
| 15 | Larynx | IVA | 6.1 | 3.7 | -39 | 10 | 4.4 | -63 | yes | yes |
| 16 | oropharynx | IVA | 15.2 | 4.6 | -70 | 5.9 | 3.7 | -37 | yes | yes |
| 17 | oropharynx | IVA | 8.9 | 9.9 | 11 | 4.9 | 9.6 | 96 | yes | yes |
| 18 | oropharynx | IVA | 8.8 | 1.9 | -79 | 7.2 | 1.7 | -77 | yes | yes |
| 19 | oropharynx | III | 8.3 | 4.4 | -47 | 0 | 0 | 0 | yes | yes |
| 20 | Larynx | IVA | 7.9 | 0 | -100 | 17.1 | 6.6 | -61 | no | no |
| 21 | oropharynx | IVA | 9.8 | 8.9 | -9 | 6.9 | 4.6 | -33 | yes | yes |
| 22 | oropharynx | IVA | 6.9 | 6.9 | 0 | 9 | 6.8 | -24 | no | yes |
| 23 | oropharynx | IVA | 5.9 | 3.8 | -36 | 4.3 | 0 | -100 | yes | yes |
| 24 | oropharynx | IVA | 9.6 | 4.6 | -52 | 8 | 5.3 | -34 | yes | yes |
| 25 | oropharynx | IVA | 7 | 5.2 | -36 | 5.6 | 5.3 | -5 | no | yes |
| 26 | oropharynx | IVA | 2.8 | 0 | -100 | 3.3 | 4.5 | 36 | yes | yes |
| 27 | oropharynx | III | 7.7 | 4.1 | -47 | 6.7 | 0 | -100 | yes | yes |
| 28 | oropharynx | IVB | 17.2 | 11.5 | -33 | 4.6 | 5.7 | 24 | yes | yes |
| 29 | oropharynx | IVB | 8.2 | 0 | -100 | 0 | 0 | 0 | yes | yes |
| 30 | oropharynx | IVA | 6.9 | 0 | -100 | 4.3 | 4.2 | -2 | yes | yes |
| 31 | oropharynx | III | 3.7 | 2.8 | -24 | 8.5 | 3 | -65 | yes | yes |
| 32 | oropharynx | III | 7.3 | 4.4 | -40 | 6.2 | 2.7 | -56 | yes | yes |
| 33 | oropharynx | IVA | 14 | 4.5 | -68 | 14.4 | 5.9 | -59 | yes | yes |
| 34 | oropharynx | IVB | 5.8 | 3.9 | -33 | 2.2 | 2.9 | 32 | no | no |
| 35 | oropharynx | IVB | 8.2 | 0 | -100 | 13.9 | 8.5 | -38.8 | yes | yes |
| 36 | oropharynx | IVB | 9.3 | 5 | -46.2 | 9.7 | 5 | -48.45 | yes | yes |
| 37 | oropharynx | III | 6.3 | 0 | -100 | 2.8 | 3.6 | 28.57 | yes | yes |
| 38 | oropharynx | IVA | 6.1 | 0 | -100 | 6.3 | 2.4 | -60.65 | yes | yes |
| 39 | oropharynx | IVA | 13.9 | 7.7 | -44.6 | 9.5 | 5 | -47.36 | yes | yes |
| 40 | oropharynx | IVB | 5.3 | 0 | -100 | 5.4 | 0 | -100 | yes | yes |
| 41 | hypopharynx | III | 13.1 | 3.2 | -75.5 | 2 | 1.6 | -20 | yes | yes |
| 42 | Larynx | IVB | 5.3 | 3.6 | -32 | 9.8 | 7.5 | -23.4 | yes | yes |
| 43 | oropharynx | IVA | 9.3 | 6.3 | -32.2 | 3.3 | 6.3 | 96.8 | no | no |
| 44 | oropharynx | IVA | 4.4 | 0 | -100 | 6.7 | 0 | -100 | yes | yes |
| 45 | oropharynx | IVB | 4.7 | 5.2 | 10.6 | 3.7 | 2.9 | -21.6 | yes | yes |
| 46 | oropharynx | IVA | 4.7 | 3.2 | -31.9 | 6.5 | 4.3 | -33.8 | yes | yes |

(*Continued*)

Table 2. (Continued)

| Patient no. | Site | Clinical Staging | $^{18}$F-FDG (max SUV)–T | | | $^{18}$F-FDG (max SUV)—N | | | Response (WHO) | Response (mWHO) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | Day 14 | Change (%) | Baseline | Day 14 | Change (%) | | |
| 47 | oropharynx | IVA | 5.8 | 3.2 | -44.8 | 3.4 | 2.3 | -32.3 | yes | yes |

Change in primary tumor and maximum standard uptake value (SUV) of regional lymph nodes after the first induction chemotherapy (IC), and WHO and mWHO criteria for each individual patient (after the second cycle of IC). N = 47.

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responsive (no increase in neck SUV) that achieved ≥45% SUV reduction in primary tumors on D14-C1-ICPET/CT (18 patients) experienced excellent outcomes, with no progressive disease or death reported.

## Discussion

Since randomized trials demonstrated the superior efficacy of TPF over PF in LASCCHN, IC followed by CBRT has re-emerged as a therapeutic option; however, TPF- associated toxicities have raised concerns about the feasibility of this approach [41–43]. Even with more powerful IC regimens, 3%–7% and 11%–12% of patients experience disease progression and stability, respectively, and may, therefore, benefit from an early change in therapeutic strategy [10–12]. This prompted a discussion regarding the potential benefit of early evaluation of tumor response, allowing selection of patients with responsive tumors to continue with function preserving approaches, while offering patients with non-responsive tumors alternative salvage treatments. Data regarding the role of early response assessment by conventional methods (endoscopy and CT scan) are scarce. Although early endoscopic examination appears to provide good prognostic information, CT is insufficiently sensitive to detect response at this time [44–46]. Hence, we investigated an alternative response evaluation method, PET/CT, early in the course of treatment.

The use of PET/CT for head and neck cancer management has increased, is considered highly reproducible [47] and presents many indications [31, 32, 48]. Additionally, early metabolic evaluation may be useful during the course of chemotherapy for esophageal cancer, Hodgkin´s lymphoma, and breast cancer [33–36].

The role of metabolic response evaluation at the time of routine tumor assessment (after two cycles of IC) has previously been reported [49–50]. PET/CT could detect distinct subgroups of patients according to the extent of SUV reduction from baseline. This approach has also been tested during IC for LASCCHN after the first cycle of chemotherapy [45, 51–53]. The discovery of metabolic parameters with enhanced prognostic discriminatory capabilities, such as metabolic tumor volume or total lesion glycolysis, has introduced another level of complexity [54–55]. Although it remains unclear which metabolic parameter or threshold is optimal for identification of responsive tumors, the results of these investigations point to a significant prognostic role for early PET/CT during induction chemotherapy. Our group has previously reported findings from a prospective study in which early changes in ADC as measured by MRI was shown to be a potential surrogate for early complete metabolic and morphological 18F-FDG PET/CT response in patients treated with IC for LASCCHN [56].

The present trial demonstrated that patients with an increase in neck SUV after the first cycle of IC experienced inferior outcomes. Furthermore, among those with no elevation in regional lymph node SUV, patients whose primary tumors demonstrated a significant (>45%) decrease in SUV after the first cycle of IC fared better in terms of PFS and OS.

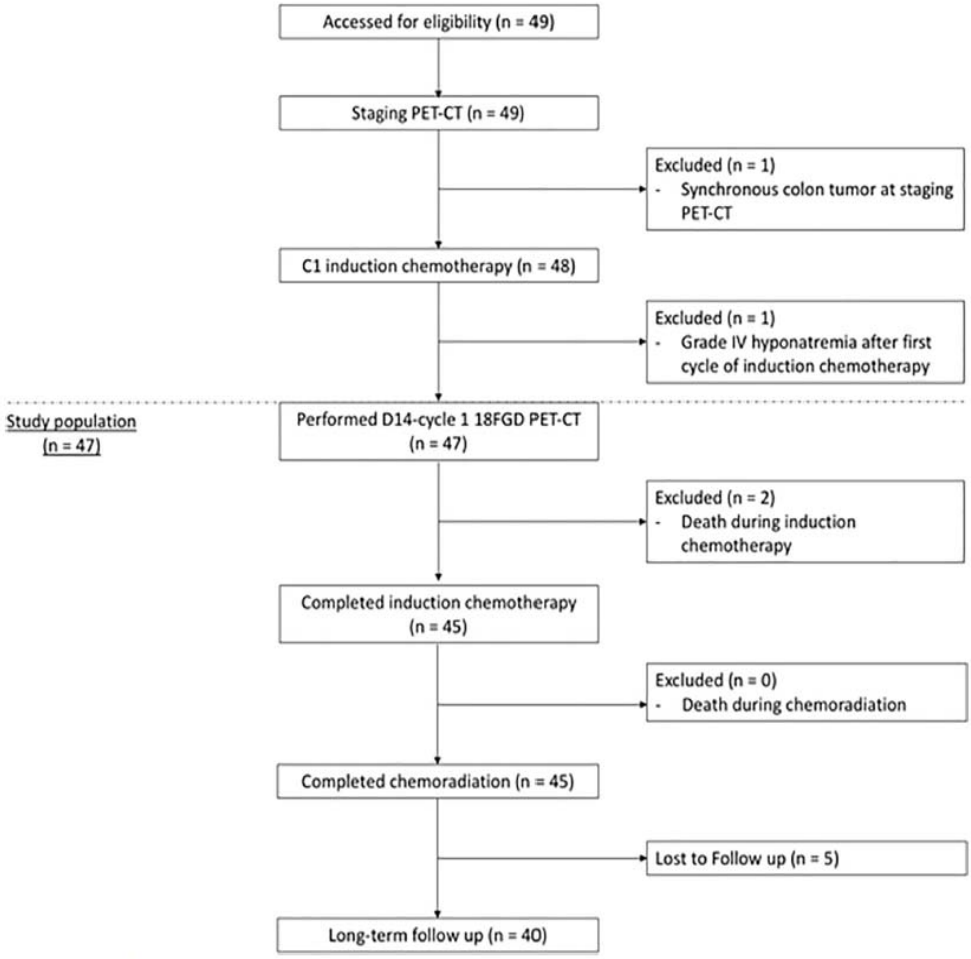


**Fig 1. The Consort flowchart descriptions of the entire study populations.**

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In our study, the prognostic information derived from D14-C1-IC $^{18}$F-FDG PET/CT was more reliable than that provided by standard morphological criteria (WHO and mWHO). While response according to PET/CT was significantly associated with PFS and OS, the relationship between response and outcomes determined using anatomical criteria was weaker or absent. This is supported by data showing that PET/CT is more accurate for defining clinical and pathological responses, relative to CT and MRI, respectively [45,46,53]. Although response by morphological criteria can predict clinical outcome and response to radiotherapy,

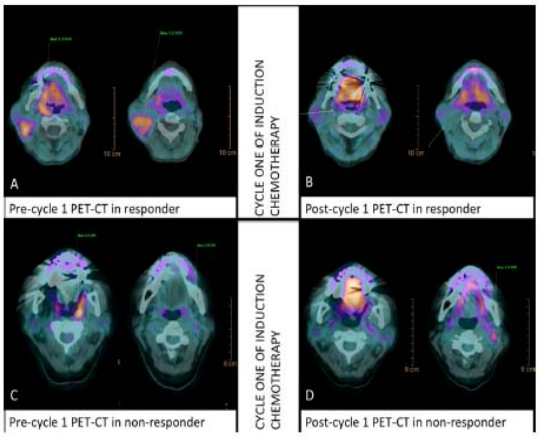


**Fig 2. Two patients presenting metabolic responsive and non-responsive tumors/ neck lymph node after once IC cycle.** Pretreatment PET/CT(A) and post-treatment PET/CT(B) in patient harboring oropharyngeal tumor with complete metabolic response at 14$^{th}$ day, cycle 1 of induction chemotherapy (SUV variation from 5.1 to 0.0 and 5.3 to 0.0 in lymph node and primary tumor respectively). Pretreatment PET/CT(C) and post-treatment PET/CT(D) in patient harboring non-responsive oropharyngeal tumor with Increased metabolic response at 14$^{th}$ day, cycle 1 of induction chemotherapy (neck lymph node SUV variation from 2.8 to 3.6, despite achieving a complete metabolic response in primary tumor).

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according to studies performed before the era of modern imaging techniques, treatment response assessment may be improved by incorporation of newer technologies, such as PET/CT [57, 58].

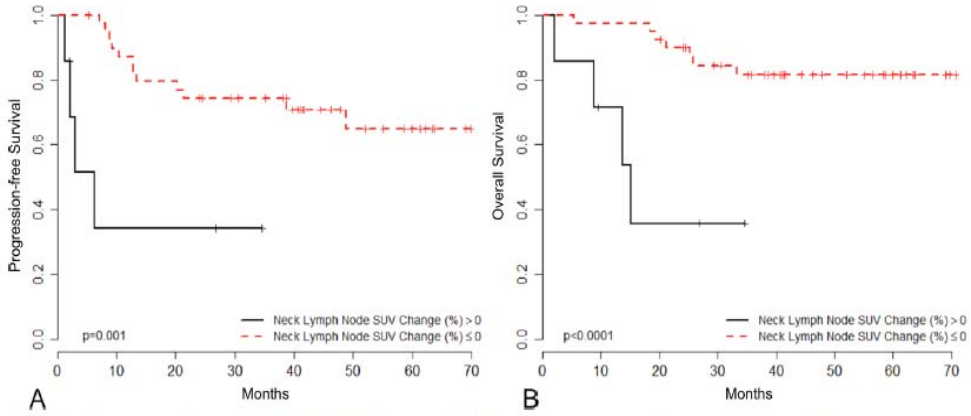


**Fig 3. Clinical outcome according to neck lymph node SUV change after cycle 1 of IC.** Progression-free survival (3A) and overall survival (3B) of patients who underwent D14-C1-IC $^{18}$F-FDG PET/CT according to the change in the maximum SUV of regional lymph nodes after the first cycle of IC (N = 47). Patients with tumors demonstrating no change or decrease in neck lymph node SUV (neck lymph node SUV change (%) $\leq$ 0) were considered responders (N = 40; red) and those with tumors showing an increase in neck uptake (Neck Lymph Node SUV Change (%) > 0) were considered non-responders (N = 7; black).

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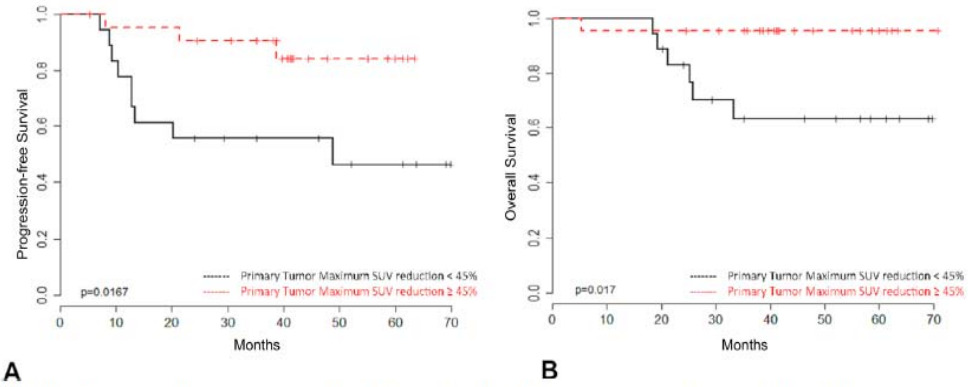


**Fig 4. Clinical outcome according to primary tumor SUV extent change after cycle 1 of IC.** Progression-free survival (4A) and overall survival (4B) among responsive patients (neck lymph node SUV change (%) ≤ 0) according to the change in maximum primary tumor SUV after the first cycle of IC (N = 40). Patients with maximum primary tumor SUV reduction ≥ 45% (N = 22; red) showed improved outcomes compared with those with primary tumor uptake reduction < 45% (N = 18; black).

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The high frequency of patients with primary oropharyngeal tumors and the absence of patients with oral cavity cancer in our study population reflect the usual clinical care adopted in our center. Common treatment modalities are IC followed by chemoradiotherapy for OPSCC and immediate surgical resection for oral cavity tumors. The preponderance of HPV-related OPSCC explains the high responsiveness and disease control recorded in our population. The rising incidence of HPV-related OPSCC and its improved prognosis have raised concerns regarding over-treatment related toxicity [22, 59, 60]. Preliminary data from ECOG

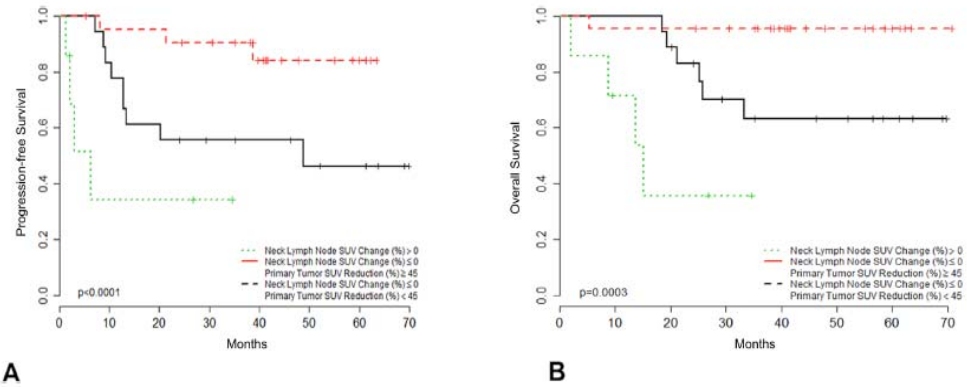


**Fig 5. Clinical outcome according to primary tumor/neck lymph node SUV change after cycle 1 of IC.** Progression-free survival (5A) and overall survival (5B) among patients according to maximum regional lymph node SUV change and primary tumor SUV change after the first cycle of induction chemotherapy (N = 47). Patients with responsive tumors (neck lymph node SUV change (%) ≤ 0) and maximum primary tumor SUV reduction ≥ 45% (N = 22; red) showed improved outcomes compared with patients with responsive tumors (neck lymph node SUV change (%) ≤ 0) and primary tumor maximum SUV reduction <45% (N = 18; black), or with patients with unresponsive tumors (neck Lymph node SUV change (%) > 0; N = 7; green).

https://doi.org/10.1371/journal.pone.0200823.g005

1308 showed promising results with low-dose RT, with patients with HPV-positive OPSCC achieving complete response to IC [61]. There is growing interest in developing tools to identify the subgroup of patients for whom treatment de-intensification can be safely applied [19, 62]. In the current trial, patients harboring HPV-related oropharyngeal cancers, whose primary tumors presented SUV decreases of $\geq$45% experienced impressive outcomes. No progressive disease or death was recorded in this subgroup, suggesting that early PET/CT could be used to select a population for treatment de-intensification.

This study has limitations. First, the criteria used to define tumors as responsive according to regional lymph node SUV change during IC have not previously been validated. Second, among those patients with responsive tumors, the cut-off for prognostication was obtained retrospectively. Third, due to the low number of events in this population, we were unable to independently evaluate the effects of different variables on treatment outcomes. Finally, data regarding HPV status was not available for all oropharyngeal cancer patients. Despite these shortcomings, to the best of our knowledge, this is the largest prospective study assessing the role of early PET/CT during IC (after the first cycle) for head and neck cancer. Additionally, interim PET/CT evaluation was performed in a blinded fashion, avoiding possible interference with patient management. Moreover, patients were treated uniformly according to standard practice, and were recruited within a narrow interval, ensuring consistent, similar patterns of care throughout the study. We think this pilot study provides important information regarding the role of early metabolic tumor-response evaluation for patients with LASCCHN that are treated with IC-CRT. However, we acknowledge our findings do not allow changing the standard clinical practice, as morphological tumor-response evaluation according to the WHO criteria after se second cycle of IC still remains the most validated method to identify patients with tumors sensitive to chemotherapy and radiation therapy. We believe that a practice-changing shift in the management of LASCCHN using metabolic tumor-response assessment during IC would rely on the results of a properly designed randomized controlled trial in which LASCCHN patients treated with IC-CRT would be randomly allocated to undergo tumor-response evaluation by the standard evaluation criteria after the second cycle of IC versus patients undergoing an early 18 FDG PET/CT after the first cycle of IC, and then managed accordingly.

To conclude, D14-C1-IC $^{18}$F-FDG PET/CT evaluation is a promising tool to identify patients with responsive tumors during IC. Further studies are necessary to confirm these findings, and explore their implications for patient management. Additionally, at a time when de-intensification of HPV-related oropharyngeal cancer is proposed, early PET/CT provides a potential tool to select those patients with tumors responsive to less aggressive treatment strategies.

## Supporting information

**S1 Table. Patients and tumor characteristics.**
(DOCX)

**S2 Table. Detailed description of staging and treatment.** This is the S2 table legend D: Docetaxel; P: Paclitaxel; C: Cisplatin; Ca: Carboplatin; F: 5-Fluoracil; Cx: Cetuximab; N/A1: not applicable (toxic death after Cycle 3 Induction Chemotherapy); N/A2 not applicable (exclusive radiotherapy post-Induction Chemotherapy).
(DOCX)

**S1 File. This is ethic committee.**
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**S3 File. TREND statement checklist: This is TREND statement checklist.**
(DOCX)

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# 5 CONCLUSÃO

A avaliação do PET-CT com D14-C1-QI FDG é uma ferramenta promissora para identificar precocemente pacientes portadores de CECLA responsivos a QI.

Adicionalmente, com a preocupação atual em se identificar pacientes de melhor prognóstico candidatos a de- intensificação de terapias utilizadas, discute-se o potencial papel de se avaliar precocemente com métidos morofo-metabólicos com uso de PET-CT pacientes portadores câncer de orofaringe relacionado ao HPV, visando selecionar aqueles pacientes com tumores responsivos que potentcialmente poderiam se beneficiar de terapias menos agressivas e com menor toxicidade aguda e tardia, sem comprometimento de sua eficácia no controle tumoral e sobrevida.

Considerando-se tratar-se de um estudo piloto, sugerimos estudos adicionais que corroborem os seus achados e os validem.

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**Anexo 1** - Carta de aprovação do Comitê de Ética em Pesquisa-CEP

Hospital A.C.Camargo
Centro de Tratamento, Ensino e Pesquisa em Câncer

**Comitê de Ética em Pesquisa - CEP**

São Paulo, 04 de Dezembro de 2009.

**PARECER CONSUBSTANCIADO**

**Projeto:** 1288/09

**Título:** "USO DO $^{18}$FDG-PET-CT COMO PREDITOR DE EFICÁCIA PARA CONTROLE LOCOREGIONAL E SOBREVIDA EM CARCINOMA EPIDERMÓIDE DE CABEÇA E PESCOÇO"

**Pesquisador Responsável:** Dr. Ulisses Ribaldo Nicolau (Departamento)

**Co-Pesquisadores:** Tadeu Ferreira de Paiva Jr, Paula Nicole Vieira Pinto, Antônio Cássio de Assis Pellizzon, Marcello Ferretti Fanelli, Eduardo Nóbrega Pereira Lima e Luiz Paulo Kowalski.

**Patrocinador:** não há

**Comentários gerais:**
O projeto é interessante, envolve um tema pouco abordado na literatura nacional, de interesse crescente pela prevalência da doença em nosso meio.

**Pendências apontadas em parecer anterior:**
1. Informar o tempo de seguimento dos pacientes uma vez que o objetivo inclui a avaliação de sobrevida livre de doença e sobrevida global numa casuística de 60 pacientes com 24 meses destinados à coleta de dados;
2. O Titulo deveria fazer referência ao uso do PET com CT;
3. Detalhara técnica específica do exame (tempos, doses, preparos e etc.) e dos critérios de resposta adotados no PET-CT (SUV máximo?, médio?, região de interesse?, Faixas de valores?, Proporção de queda? e etc.).

**Comentários Finais:**
Após análise das respostas aos questionamentos apontados em parecer anterior, consideramos que todas as pendências foram atendidas. Portanto, decidimos pela aprovação final do projeto em referência.

**Parecer Final:**
Projeto Aprovado.

**Dr. Alexandre Sá de Andrade**
**2º Vice-Coordenador do Comitê de Ética em Pesquisa**

**Apêndice 1** - Termo de Consentimento Livre e Esclarecido-TCLE

**Hospital A.C.Camargo - Fundação Antônio Prudente**
**Rua Professor Antonio Prudente, 211** **Telefone : (011) 2189-5000**
**São Paulo-SP CEP: 01509-010**

**CONSENTIMENTO PÓS-INFORMADO**

(Obrigatório para Pesquisa Clínica em Seres Humanos- Resolução no 196/96 e resolução CNS 252/97 do Ministério da Saúde)

Este termo está sendo solicitado exclusivamente para participação nesta pesquisa, sem possibilidade de extensão da mesma autorização para outros projetos.

PROJETO: **USO DO PET-SCAN COMO PREDITOR DE EFICÁCIA PARA CONTROLE LOCOREGIONAL EM CARCINOMA EPIDERMÓIDE DE CABEÇA E PESCOÇO.**

1. Dados de identificação do paciente ou responsável legal

Nome do(a) paciente : _____

Sexo : masculino ( ) feminino ( ) Data de nascimento _/_/_

Documento de identidade no: _____

Endereço:_____

Cidade:_____Estado:_____

CEP:_____ Tel.:_____

Responsável: _____

Sexo : masculino ( ) feminino ( ) Data de nascimento _/_/_

Documento de identidade no: _____

Endereço:_____

Cidade:_____Estado:_____

CEP:_____ Tel.:_____

2. Objetivos do estudo

Você foi convidado a participar deste estudo em câncer de cabeça e pescoço. O tratamento do câncer de cabeça e pescoço localmente avançado é baseado em quimioterapia com cisplatina e 5-fluoro-uracil concomitante a taxanes seguido de

radioterapia concomitante ou não a quimioterapia. O Corpo Clínico do Departamento de Oncologia Clínica do Hospital AC Camargo está desenvolvendo pesquisa clínica na área de câncer de cabeça e pescoço localmente avançado submetidos a tratamento padrão de quimioterapia (cisplatina e 5-fluro-uracil associado a taxane) seguido de radioterapia concomitante ou não a quimioterapia. O objetivo é identificar fatores de resposta precoce ao tratamento e futuramente correlacionar com sobrevida livre de recaída com exames de imagem funcional (PET-CT) e comparar com a tomografia computadorizada, exame de imagem tradicional para avaliar resposta ao tratamento.

3. Descrição do procedimento e duração da participação no estudo

Constitui rotina no Departamento de Oncologia Clínica o esquema de tratamento proposto neste estudo, assim como os exames laboratoriais e de imagem convencionais propostos, não sendo considerado nenhum experimento. Será solicitado adicionalmente realização de exame PET-CT, que é um exame de imagem que associa imagens de metabolismo da glicose com imagens anatômicas da tomografia computadorizada sem contraste, pré terapia, após o 1º ciclo de quimioterapia e após o término da radioterapia. Serão 3 ou 4 ciclos de quimioterapia a cada 21 dias cada. Você sairá do estudo caso apresente progressão da doença ou toxicidade que impeça a continuação da terapia. O PET-CT é experimental nesse estudo, porém não é experimental na oncologia, já fazendo parte da propedêutica diagnóstica oncológica, realizado no Departamento de Imagem/ Medicina Nuclear da mesma instituição e com risco baixo de complicações inerentes ao exame. No dia da realização do exame, em jejum, você receberá a administração venosa de um material específico e encomendado previamente que é denominado 18F-FDG e produzido pelo IPEN-CNEN-SP. Este material é utilizado regularmente no setor de Medicina Nuclear para a realização deste exame sem quaisquer complicações e será doado pelo IPEN para a realização do exame. Antes da injeção venosa do 18F-FDG você terá a glicemia verificada através da realização de um exame denominado hemoglicoteste que utiliza punção capilar digital para certificar-se de que a glicemia encontra-se em níveis menores do que 200 mg/dl, pois acima destes valores a qualidade do exame pode estar prejudicada.

Você deverá dispor de pelo menos 3 horas do seu dia para a realização do exame previamente marcado, pois deverá permanecer cerca de 30 minutos em

repouso antes da injeção do 18F-FDG, aguardar cerca de 90 minutos para iniciar o exame após a injeção do 18F-FDG e cerca de 50 minutos a 1 hora para a obtenção das imagens do exame e verificação da sua qualidade técnica. Ressalto, porém, que este período poderá ser estendido se houver atraso no horário de entrega do material à instituição e há orientação rotineira no agendamento deste exame no setor aos pacientes que realizam este tipo de exame para que não assumam compromissos com horários previstos neste dia.

Riscos potenciais

Riscos inerentes do tratamento habitual, mesmo não participando desse protocolo:

Efeitos colaterais mais freqüentes pelo uso de quimioterapia:

-Docetaxel: náuseas, vômitos, mucosite, queda de glóbulos brancos e infecção, dor muscular e queda de cabelo.

-5 fluoraucil: mucosite, diarréia, síndrome palmo-plantar, pancitopenia, isquemia miocárdica, queda de cabelo grau leve

-Cisplatina: náusea, vômito, toxicidade renal, toxicidade auditiva, neuropatia, isquemia, queda de glóbulos vermelhos, queda de glóbulos brancos ou de plaquetas.

-Carboplatina: náusea, vômito, toxicidade renal, toxicidade auditiva, queda de glóbulos vermelhos, queda de glóbulos brancos ou de plaquetas.

Efeitos colaterais relacionados com a Radioterapia:

-mucosite, infecção odontogênica, dermatite ou necrose óssea.

Efeitos relacionados a tomografia computadorizada:

- reação alérgica ao contraste, flebite.

Quanto ao PET-CT, que será o único procedimento adicional ao padrão de terapia e exames que o paciente normalmente receberia fora do estudo, os riscos previstos são aqueles envolvidos com a sensação de dor que poderá ocorrer quando for realizada a punção capilar digital com agulha de insulina para a verificação da glicemia e na punção venosa com escalpe para a injeção do 18F-FDG. Há, ainda, o risco de extravasamento dérmico do material injetado venosamente mas , que caso ocorra, não implicará em nenhuma lesão de órgão e, também, o risco de possível infecção após as punções citadas, mas que são minimizadas com assepsia adequada.

Pacientes do sexo feminino, em idade fértil, devem assegurar que não engravidarão durante a terapia devido ao potencial teratogênico das drogas e da radiação (exames de imagem), portanto assumindo os riscos da gestação , caso venha a acontecer.

Benefícios previstos

A participação neste estudo tem como propósito melhorar a abordagem de tratamento dos pacientes com câncer de cabeça e pescoço localmente avançados. Caso você concorde em participar do estudo pode haver ou não benefício direto para você. Esperamos que as informações obtidas neste estudo com a inclusão do método de imagem (PET-CT) precocemente na avaliação destes pacientes permita identificar pacientes que realmente se beneficiarão do tratamento quimioterápico seguido por radioterapia e, em estudos futuros, isto possa ser confirmado e evitar toxicidade adicional desta drogas em pacientes que não obtenham a resposta adequada esperada com o tratamento inicial instituído.

Tratamentos alternativos ao objeto da pesquisa

Quando optado pelo tratamento quimioterápico seguido de radioterapia associado ou não a quimioterapia, os esquemas e doses serão os tradicionais utilizados na nossa instituição. O tratamento oferecido não está em teste.

Salvaguarda de confidencialidade, sigilo e privacidade

A eventual inclusão dos resultados em publicação científica será feita de modo a manter seu anonimato. Você terá acesso aos seus dados de exames, atendimentos médicos e administração de terapia, quando solicitados.

Esclarecimentos sobre compensações ou danos relacionados à pesquisa

Você não terá nenhum tipo de remuneração ao aceitar participar deste estudo. A pesquisa não envolve nenhuma forma de compensação financeira aos participantes. Não existe nenhum tipo de indenização para complicações causadas pelo tratamento.

Esclarecimentos sobre outros direitos do paciente sujeito à pesquisa

A sua participação no estudo é voluntária. Você tem o direito de sair do estudo a qualquer momento e por qualquer motivo. Caso venha a abandonar o

estudo ou decidir não participar do mesmo, o seu tratamento não será prejudicado. No entanto, se você decidir sair da pesquisa, deverá informar ao seu médico.

O Comitê de Ética Médica do Hospital A. C. Camargo é o responsável legal para a certificação de que os direitos dos pacientes estejam protegidos. Este comitê analisou e aprovou este estudo.

Informações sobre nomes, telefones e endereços para contatos

Esclarecimentos para questões sobre os direitos dos participantes na pesquisa e/ou danos relacionados à pesquisa, contatar os pesquisadores Dr Ulisses Ribaldo Nicolau (011) 99011147 ou 21895000 r 1551 ou Dr Tadeu Ferreira de Paiva Júnior (011) 84913815 ou 21895000 r 1551. Se o pesquisador principal não fornecer as informações/ esclarecimentos suficientes, por favor, entre em contato com o coordenador do Comitê de Ética do Hospital A. C. Camargo-SP, pelo telefone: 2189-5020.

Você receberá cópia deste documento e o original será arquivado no prontuário do médico. Somente assine este documento se consentir integralmente com seus termos.

**Consentimento Livre e Pós-informado**

Eu declaro que li e compreendi o procedimento. Declaro também que discuti este procedimento com meu médico. Eu entendo o propósito do estudo e os métodos que serão utilizados. Entendo também que a minha entrada neste estudo é voluntária.

Assinatura do (a) paciente ou responsável legal _____

Data: ____/ ____ /____

Nome do(a) paciente _____ RG _____

**DECLARAÇÃO DO MÉDICO OBTENDO CONSENTIMENTO PÓS-INFORMADO**

Eu declaro que expliquei este procedimento, com todos os detalhes necessários para o(a) paciente (ou seu responsável legal) _____.

No meu julgamento, houve acesso a todas as informações disponíveis, incluindo os riscos e benefícios para que se possa fazer uma decisão informada.

Assinatura do Médico _____ Data: _____ / ____ / ____