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Study Title: p-PHOTOLARYNX- ANTHEM: Pilot Photon-Counting CT Evaluation of the Paraglottic Space and Cartilage involvement in T2-T3 Laryngeal Cancer

Version No. (Date): Version 1.0 – 15.05.2025

Sponsor (Institution):
Humanitas Univeristy, Via Rita Levi Montalcini 4, Pieve Emanuele (Milano), 20090

Enrolling Center:
Department of Radiology, Department of Otorhinolaryngology
IRCCS Istituto Clinico Humanitas – Humanitas Mirasole S.p.A.
Via Manzoni 56, Rozzano (Milano), 20089

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Abbreviations

Here are the abbreviations in alphabetical order:

1. PGS :paraglottic space
2. MRI: Magnetic Resonance Imaging
3. AE: Adverse Event
4. AUC: Area Under the Curve
5. CdTe: Cadmium Telluride
6. CNR: Contrast-to-Noise Ratio
7. CT: Computed Tomography
8. CTCAE: Common Terminology Criteria for Adverse Events
9. HU: Hounsfield Units
10. ICC: Intraclass Correlation Coefficient
11. ICF: Informed Consent Form
12. kVp: Kilovolt Peak
13. NPV: Negative Predictive Value
14. PCCT: Photon-Counting Computed Tomography
15. PPV: Positive Predictive Value
16. ROC: Receiver Operating Characteristic
17. SAE: Serious Adverse Event
18. SNR: Signal-to-Noise Ratio
19. SNR: Signal-to-Noise Ratio (used twice in the text with the same meaning)
20. SOP: Standard Operating Procedures
21. SS-SECT: Single-Source Multi-Slice Computed Tomography
22. SECT: Single-energy Multi-Slice CT (SECT)

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1. SUMMARY

Study Title	**p-PHOTOLARYNX- ANTHEM: Pilot Photon-Counting CT Evaluation of the Paraglottic Space and cartilage involvement in T2-T3 Laryngeal Cancer**		
Study code		**Acronym:-**	**p-PHOTOLARYNX ANTHEM**
Version and Date	*Versione 1.0, 15-05-25*		
Sponsor (Institution)	Humanitas Univeristy, Via Rita Levi Montalcini 4, Pieve Emanuele (Milano), 20090		
Coordinating Investigator	Caterina Giannitto		
Unit Involved	Department of Radiology, Department of Otorhinolaryngology IRCCS Istituto Clinico Humanitas – Humanitas Mirasole S.p.A. Via Manzoni 56, Rozzano (Milano), 20089		
Supporter	ANTHEM Project		
Product Name	-		
Study indication	• Patients with a highly clinically biopsy-proven T2 or T3 glottic and supraglottic laryngeal carcinoma who need to undergo further imaging evaluation either to pre-surgical assessment or to confirm the diagnosis, as per surgeon recommendation.		
Study population	• 60 patients total with biopsy-proven clinically suspected T2 or T3 glottic and supraglottic laryngeal carcinoma		
Background and rationale	Laryngeal cancer represents a significant clinical challenge due to its impact on phonation, swallowing, and airway patency. Accurate staging is paramount for tailoring appropriate therapy, particularly for T2 and T3 glottic and supraglottic tumors, where the extent of paraglottic space (PGS) involvement can shift treatment strategy from conservative approaches to radical surgery. T2 tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis without fixation of the larynx. T3 Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage, a distinction that often remains subtle on imaging but has profound implications in the selection of surgical versus non-surgical treatments.		

	For example, T1 and superficial T2 lesions can often be managed with transoral laser microsurgery or radiation alone, preserving organ function. In contrast, PGS involvement in T3 tumors, particularly with partial cartilage erosion or early fixation, may necessitate open partial laryngectomy or even total laryngectomy according to the volume of the lesion. Thus, the accurate detection of early PGS invasion is critical in multidisciplinary decision-making. Assessing inner cortex involvement in non-ossified thyroid cartilage is challenging with conventional CT due to poor visualization, and with MRI due to limited resolution and nonspecific signal changes. Photon-Counting CT (PCCT) overcomes these limitations by offering ultra-high spatial resolution and spectral imaging, allowing clearer visualization of non-ossified cartilage, better edge definition, and more accurate detection of early cartilage invasion—leading to improved staging and treatment planning in laryngeal cancer. Currently, MRI with surface coils is considered the gold standard for soft tissue staging of laryngeal cancer, due to its superior contrast resolution in delineating the boundaries of the PGS, pre-epiglottic space, and cartilage. However, this technique is costly, time-consuming, and often limited by motion artifacts, swallowing, and contraindications in patients with implants or claustrophobia. Moreover, its accessibility is limited in some clinical settings, potentially delaying staging and treatment. Conventional CT (SECT) remains widely used, especially in preoperative surgical planning, due to its availability and fast acquisition. However, it lacks the soft tissue contrast and often suffers from beam-hardening artifacts caused by the laryngeal framework. Additionally, its limited spatial resolution hinders the evaluation of subtle changes in the PGS. **Photon-Counting Computed Tomography (PCCT)** offers a novel solution to these limitations. PCCT detects and counts individual X-ray photons and records their energy, unlike traditional CT systems which use energy-integrating detectors. This allows: • **Ultra-high spatial resolution**, useful for assessing thin structures like the thyroid cartilage and paraglottic fat planes • **Spectral imaging**, enabling material decomposition and better soft tissue characterization • **Improved CNR and SNR**, reducing noise and enhancing delineation between tumor and normal tissue • **Lower radiation dose**, **Significant reduction of metal and beam-hardening artifacts**These features may allow PCCT to bridge the diagnostic gap between CT and MRI, especially in situations where MRI is contraindicated or not

	available, offering a **f**ast, accessible, and cost-effective imaging modality for accurate PGS evaluation. **RATIONALE** In the staging of T2-T3 glottic cancers, the evaluation of paraglottic space infiltration plays a pivotal role in determining eligibility for organ-preserving treatment strategies. The lack of accurate assessment may result in undertreatment (with residual disease) or overtreatment (with unnecessary laryngectomy). While MRI provides excellent contrast and soft tissue differentiation, its limitations in terms of spatial resolution, motion sensitivity, and cost reduce its utility in some settings. In contrast, PCCT promises enhanced spatial resolution and material characterization that could allow precise assessment of: • Tumor extension into the paraglottic space • Thyroid cartilage erosion, non-ossified cartilage evaluation • Differentiation between tumor, fat, edema, and inflammation • Detection of small tumor foci undetectable on SECT This study aims to prospectively evaluate PCCT as a diagnostic tool for the imaging of T2-T3 laryngeal cancer, particularly in the evaluation of the paraglottic space and cartilage involvement.
Study Objectives	**Primary Objective:** • To assess the diagnostic accuracy of PCCT in detecting PGS invasion and cartilage invasion in T2-T3 laryngeal cancer, using surgical findings and histology consensus as the reference standard. **<u>Secondary Objectives:</u>** • To assess the PCCT parameters that are regarded superior compared to conventional CT such spatial resolution of PCCT, focusing on visualization of paraglottic space and delineation of cartilage involvement. • To assess quantitative imaging parameters (HU, SNR, CNR) • To analyze the correlation between PCCT imaging parameters and SECT and MRI findings in the same cohort of patients • To gather radiologist feedback on diagnostic quality and utility using a Likert scale, comparing PCCT and MRI. • To evaluate inter-reader agreement (ICC)

	• To assess the potential for reduced radiation exposure with PCCT while maintaining or improving diagnostic accuracy
Study Endpoints/Outcomes	**Primary Endpoints**: To assess how accurately PCCT identifies true positive and true negative cases of PGS invasion and cartilage invasion, using surgical findings and histology as the gold standard. **Secondary Endpoints:** Evaluating whether PCCT maintains or improves diagnostic accuracy while reducing radiation exposure. We will assess spatial resolution analyzing the ability of PCCT to visualize fine anatomical details, particularly in the PGS and cartilage involvement-. Analyzing how well PCCT spectral imaging correlates with MRI in the same cohort of patients considered for the study, in differentiating tumour from surrounding tissues. Hounsfield Units (HU) SNR and CNR will be measured to assess the imaging quality between PCCT to better characterize various tissue types, particularly focusing on PGS involvement. Perceived diagnostic quality (including artifact reduction) will be evaluated using a Likert scale by radiologists. The PCCT imaging obtained will be compared with MRIs exams performed on the same cohort of patients**,** to evaluate PCCT improvements in diagnostic performance and image quality. Data from MRIs will only be used with the patients' prior consent. No other retrospective analysis will be conducted.
Study design	Prospective, single center, longitudinal study
Eligibility Criteria	**Inclusion Criteria:** • Adults (≥18 years) • Biopsy-proven and clinically suspected T2 or T3 glottic and supraglottic carcinoma • Candidate for surgical staging • Able to undergo PCCT **Exclusion Criteria:** • Pregnancy or breastfeeding

	• Renal failure • Severe claustrophobia Refusal of informed consent
Study Procedures	**Baseline or Pre-operative CT** • Patient will undergo a pre-operative PCCT with contrast media as per normal clinical practice on a photon-counting computed tomography. Previously acquired SECT and MRI will be included if available. (see the complete note in the text: paragraph 9.2)
Number of patients (planned)	A total of sixty patients, with biopsy-proven and clinically suspected T2 or T3 carcinoma will be enrolled in the study.
Investigational Sites (planned)	**Single-centre study X** Multi-centre study □ The centers involved in the study will be: IRCCS Humanitas Research Hospital and will involve Radiology Department and Otorhinolaryngology department.
Sample size and statistical consideration	This study involves sixty patients and will assess the diagnostic accuracy of Photon-Counting CT (PCCT). Shapiro-wilk test will be perfumed for assessing the distribution and Bonferroni correction will be applied for multiple testing. Metrics such as sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) will be calculated, using surgical findings as the gold standard. Receiver Operating Characteristic (ROC) curves will be used to evaluate the performance with McNemar's test comparing sensitivity and specificity between PCCT, and MRI or SECT Intraclass Correlation Coefficient (ICC) will assess the consistency among radiologists. Bland-Altmann analysis will be performed for hounsfield units (HU) and Contrast-to-Noise Ratio (CNR). The prospective data from PCCT will be compared with MRIs data from the same cohort of patients, when available, to evaluate and compare the potential advantages of PCCT in diagnostic accuracy, effectiveness and image quality.

Study timetable	Study duration is planned to be 2 years. Provide the following study milestones: ● Planned date of the First Patient In (FPI - date of the Informed Consent signature of the first study patient): September 2025 ● Planned date of the Last Patient In (LPI - date of the Informed Consent signature of the last study patient): October 2027 ● Planned date of the Last Patient Out (LPO – date of the last visit of the last study patient): November 2027 ● Data analysis: Planned study duration (from FPI to LPO): 2 years
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki and applicable guidelines as well as all national legal and regulatory requirements.

2. STUDY FLOW-CHART

Event		
DAy	Enrollment	T_0
Inclusion/exclusion criteria check	X	
Informed consent	X	
Demographic data	X	
Anamnesis	X	
Baseline Photon Counting CT		X

3. BACKGROUND

Laryngeal cancer represents a significant clinical challenge due to its anatomical complexity, critical functional implications, and the heterogeneity of its presentation and progression. The larynx, being central to phonation, swallowing, and airway protection, becomes a site where tumors—especially those in the glottic region—pose serious threats to both survival and quality of life. Among the glottic and spraglottic cancers, T2 and T3 lesions are particularly pivotal, as they represent a transitional stage where treatment choices can vary widely based on subtle imaging findings.

Accurate staging of glottic cancer is essential in tailoring therapeutic strategies. The therapeutic spectrum ranges from minimally invasive organ-preserving techniques to radical procedures such as total laryngectomy. A key determinant in this spectrum is the evaluation of paraglottic space (PGS) involvement. The PGS, a fat-containing region adjacent to the vocal cords, acts as a conduit for tumor spread in both the vertical and lateral planes. Its infiltration is associated with poorer outcomes and often necessitates more aggressive surgical interventions. Thus, the early and accurate detection of tumor extension into the PGS is of paramount importance in treatment planning.

In the current TNM classification, T2 laryngeal cancer is defined by extension of the tumor into the supraglottic or subglottic regions, and T3 by involvement of PGS or inner cortex of thyroid cartilage and/or impaired vocal cord mobility.. Failure to detect PGS involvement may lead to inadequate treatment, such as radiation or endoscopic resection when more extensive surgery is warranted. Conversely, overestimation of tumor spread may lead to unnecessary radical procedures with significant morbidity.

Assessing inner cortical involvement of the thyroid cartilage remains one of the most difficult challenges in laryngeal imaging, particularly in younger patients or in areas where the cartilage has not yet undergone physiological ossification. Non-ossified cartilage, being radiolucent, is poorly visualized on conventional CT, making it nearly impossible to determine whether the tumor is abutting or infiltrating the inner cortex. This limitation becomes critical in the staging of T2–T3 glottic cancers, where subtle cartilage invasion can upstage the tumor to T4a, altering the treatment plan significantly. While MRI provides better soft tissue contrast, it often lacks the spatial resolution needed to confidently evaluate the thin inner cortical margin, and signal changes within cartilage can be nonspecific, overlapping with inflammation, fibrosis, or early tumor.

Photon-Counting CT (PCCT), with its ultra-high spatial resolution and spectral imaging capabilities, offers a promising solution. PCCT enhances the visualization of fine bony and cartilaginous structures, even in areas of partial or absent ossification, by reducing noise and increasing contrast-to-noise ratios. Its ability to generate virtual monoenergetic images and perform material decomposition may help distinguish tumor tissue from cartilage, even when the latter is unossified. Additionally, PCCT’s improved edge definition allows for more confident detection of subtle erosions or demineralization along the inner cortex, which may indicate early invasion. By enabling more accurate characterization of cartilage integrity, PCCT may significantly improve the

staging precision of laryngeal cancers and help avoid both undertreatment and overtreatment in equivocal cases.

For instance, T1 and superficial T2 glottic tumors are often managed with transoral laser microsurgery (TLM) or definitive radiation therapy, preserving the organ and function. These approaches are associated with excellent local control and voice outcomes when appropriately selected. However, once the tumor invades the PGS or shows signs of early thyroid cartilage erosion, the likelihood of recurrence with conservative therapy increases significantly. In such cases, open partial horizontal laryngectomy (OPHL) or even total laryngectomy may be indicated. Thus, the role of imaging becomes central not just in staging, but in dictating the entire therapeutic trajectory.

Magnetic resonance imaging (MRI) with surface coils is currently regarded as the gold standard for soft tissue evaluation of the larynx. Its excellent contrast resolution allows clear delineation of the paraglottic and pre-epiglottic spaces, as well as detailed assessment of cartilage involvement. DWI sequences can help assess cord mobility, while fat-suppressed T2-weighted and contrast-enhanced sequences assist in differentiating tumor from edema or inflammation. However, MRI is not without limitations. It is time-consuming, prone to motion artifacts due to swallowing and breathing, and contraindicated in patients with certain implants, pacemakers, or claustrophobia. In addition, in some healthcare settings, access to high-quality laryngeal MRI remains limited due to logistical and economic constraints.

Conventional single-energy computed tomography (SECT) continues to be widely used in clinical practice, especially in the preoperative setting. SECT is rapid, widely accessible, and highly effective in detecting gross cartilage erosion. However, its role in soft tissue delineation, particularly within the larynx, is limited. The lack of inherent contrast between tumor and adjacent fat, edema, or inflammation hinders its accuracy in evaluating the PGS. Furthermore, SECT suffers from beam-hardening artifacts, especially from dental amalgams and laryngeal cartilage calcifications, which further reduce image quality.

In this context, Photon-Counting Computed Tomography (PCCT) emerges as a transformative imaging modality with the potential to redefine laryngeal imaging. Unlike traditional CT scanners that use energy-integrating detectors, PCCT employs photon-counting detectors capable of counting individual X-ray photons and measuring their energy. This fundamental technological shift brings several advantages that are particularly pertinent to the evaluation of laryngeal cancer:

1. **Ultra-high spatial resolution:** PCCT can achieve spatial resolutions below 0.2 mm, which is especially beneficial in assessing the thin fat planes of the PGS and subtle erosions of the thyroid cartilage. This resolution may surpass both SECT and, in some aspects, even MRI in anatomic detail.

2. **Spectral imaging capabilities:** PCCT provides simultaneous multi-energy imaging, enabling material decomposition and virtual monoenergetic imaging. These features allow for enhanced soft tissue contrast and improved differentiation of tumor from surrounding structures such as muscle, fat, or inflamed tissue.

3. **Improved contrast-to-noise (CNR) and signal-to-noise ratio (SNR):** The detection of individual photons and rejection of electronic noise lead to cleaner, more interpretable images, particularly critical in the densely packed anatomical landscape of the larynx.

4. **Reduced radiation dose:** PCCT achieves these enhancements while maintaining or even reducing radiation exposure, which is crucial in head and neck oncology patients who often undergo repeated imaging for follow-up.
5. **Artifact reduction:** Beam-hardening and metallic artifacts, common issues in conventional CT, are significantly reduced with PCCT..

These technological advantages suggest that PCCT could bridge the diagnostic gap between SECT and MRI, particularly for evaluating the paraglottic space. In scenarios where MRI is contraindicated, unavailable, or inconclusive, PCCT could provide a reliable alternative, offering high-resolution, fast, and reproducible imaging.

4. RATIONALE

In the staging of T2–T3 glottic cancers, precise evaluation of the PGS is essential. As discussed, the presence or absence of PGS invasion can drastically alter the therapeutic approach. A false-negative interpretation might lead to under-treatment, resulting in recurrence and the need for salvage surgery. On the other hand, a false-positive diagnosis could lead to unnecessarily aggressive surgery with substantial impact on voice and quality of life.
The limitations of SECT in this context are well documented. Its inferior soft tissue contrast, combined with metal artifacts and suboptimal spatial resolution, may lead to misinterpretation of tumor extent. In contrast, while MRI excels in soft tissue delineation, it may struggle with spatial resolution, be affected by motion artifacts, and suffer from limited accessibility in some clinical settings.
PCCT, therefore, represents a promising modality that may offer the best of both worlds: the accessibility and speed of CT, coupled with resolution and contrast characteristics approaching those of MRI. Its spectral imaging capabilities may allow for refined tissue characterization, distinguishing tumor from inflammation or fibrosis, a frequent challenge in both staging and post-treatment surveillance.
Specifically, PCCT may enhance:

- **Detection of early PGS invasion:** Subtle extensions of tumor into the paraglottic fat are often difficult to detect on SECT. PCCT’s resolution and contrast may reveal early invasion with greater sensitivity.

- **Assessment of thyroid cartilage involvement:** PCCT can improve the visualization of cortical erosion and marrow changes within the thyroid cartilage. This is critical for staging, as cartilage invasion often upgrades the tumor to T4a.

- **Differentiation of tumor vs. post-radiation changes:** In the post-treatment setting, fibrosis, edema, and residual tumor may coexist. PCCT's ability to perform virtual non-contrast and spectral analysis could help distinguish these entities.

- **Visualization of small tumor foci:** Tiny tumor extensions that escape detection on SECT or are equivocal on MRI may be visible on high-resolution PCCT scans

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Moreover, PCCT could be particularly valuable in patients with MRI contraindications such as those with cochlear implants, pacemakers, or severe claustrophobia—and in institutions where MRI resources are limited or overloaded. The fast acquisition time, lower cost per exam compared to MRI, and potential for integration with other spectral imaging techniques make PCCT a highly appealing candidate for routine clinical practice in head and neck oncology.

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5. STUDY OBJECTIVES.

5.1. Primary Objectives:

Primary Objectives:

- To assess the **diagnostic accuracy** of PCCT in detecting paraglottic space invasion and cartilage invasion in T2-T3 laryngeal cancer, using surgical findings and histology consensus as the reference standard.

5.2 Secondary Objectives:

Secondary Objectives:

- To assess the PCCT parameters that are regarded superior compared to conventional CT such spatial resolution of PCCT, focusing on visualization of paraglottic space, delineation of cartilage involvement.

- To assess quantitative imaging parameters (HU, SNR, CNR)

To analyze the correlation between PCCT imaging parameters and MRI findings in the same cohort of patients

- To gather radiologist feedback on diagnostic quality and utility using a Likert scale, comparing PCCT and MRI.

- To evaluate inter-reader agreement (ICC)

To assess the potential for reduced radiation exposure with PCCT while maintaining or improving diagnostic accuracy.

Imaging data from the same cohort of patients who will receive MRI will be compared with the results from this prospective PCCT study to evaluate improvements in diagnostic performance and image quality.

6. Study Endpoints

6.1. Primary Outcome Measures

To assess how accurately PCCT identifies true positive and true negative cases of PGS invasion and cartilage invasion, using surgical findings and histology as the gold standard.

6.2. Secondary Outcome Measures

Secondary outcome measures will include:

- Evaluating whether PCCT maintains or improves diagnostic accuracy while reducing radiation exposure.
- We will assess spatial resolution analyzing the ability of PCCT to visualize fine anatomical details, particularly in the PGS and cartilages.
- Analyzing how well PCCT spectral imaging correlates with MRI in the same cohort of patients considered for the study, in differentiating tumour from surrounding tissues.
- Hounsfield Units (HU) SNR and CNR will be measured to assess the imaging quality between PCCT to better characterize various tissue types, particularly focusing on PGS and cartilage involvement.
- Perceived diagnostic quality (including artifact reduction) will be evaluated using a Likert scale by radiologists.

The PCCT imaging obtained will be compared with previous traditional SECTs or MRIs exams performed on the same cohort of patients, when available, to evaluate PCCT improvements in diagnostic performance and image quality.

Data from previous SECTs or MRIs will only be used with the patients' prior consent.

No other retrospective analysis will be conducted

7. Study Population

A total of sixty patients, with biopsy-proven and SECT/MRI suspected T2 or T3 glottic carcinoma will be enrolled in the study.

8. SELECTION CRITERIA

8.1. Inclusion Criteria

- Adults (≥18 years)
- Biopsy-proven and SECT/MRI suspected T2 or T3 glottic and supraglottic carcinoma
- Candidate for surgical staging

Able to undergo PCCT

8.2. Exclusion criteria

- Pregnancy or breastfeeding
- Renal failure
- Severe claustrophobia
- Refusal of informed consent

9. STUDY DESIGN

The results of the present prospective observational study, aim to assess the diagnostic accuracy of PCCT in detecting PGS invasion and Thyroid cartilage involvement in T2-T3 laryngeal cancer, using surgical findings consensus as the reference standard.
Data will be also compared with those obtained from single-energy CT (SECT) and MRI in the same cohort of patients. This comparison aims to evaluate the diagnostic accuracy, sensitivity, specificity, and overall effectiveness of PCCT relative to the traditional imaging methods. Such analysis will provide a historical control that allows for a direct assessment of the potential advancements offered by PCCT in the diagnosis and management of laryngeal cancer.

9.1. Enrollment:

Candidate patients will be screened from the patient population of the study site, and they will be invited to participate in the p-PHOTOLARYNX-ANTHEM Study. Prior to inclusion in the study the

patient will receive complete information about the aim of the study both orally and in writing. Written informed consent for study participation and the use of personal data must be obtained.
Upon presentation of the ICF, clinical history, demographic data, physical examination and vital signs of subjects will be collected to determine eligibility.
Preexisting adverse conditions and concomitant medications will be investigated through accurate anamnesis enrollment (see also selection and exclusion criteria) in the study.

9.2. Baseline or pre-operative CT

Patient will undergo a baseline/pre-operative CT with iodinate contrast media as per normal clinical practice on a photon-counting computed tomography.

Our study includes patients requiring additional imaging to confirm clinical or radiological suspicion of disease, as well as those for whom a pre-operative CT scan has been recommended by the surgeon. In cases of laryngeal T2-T3 carcinoma , an MRI remains essential.for accurate surgical planning. The patient will undergo MRI in accordance with current guidelines, with the examination covered by the National Health Service (SSN).

9.3. End of study Definition

A subject is considered to have completed the study if he/she has completed the baseline/pre-preoperative on the PCCT and MRI. End of the study will be reached after the last patient enrolled (see Sample size).
Data collection will be started from patient n°1, finished after having collected data from the last patient. Data analysis will be performed during and after the course of the study.
The end of the study will occur when the last subject enrolled completes their PCCT

9.4. Study Discontinuation

A participant may withdraw from the study at any time at his/her request or may be withdrawn at any time at the discretion of the Investigator

The reason for withdrawal will be investigated and carefully documented in the Patient’s Medical file and the appropriate section of the Case Report Form

10. STUDY ASSESSMENT

For this study our priority is to provide patients with the all the information necessary.
Subjects from IRCCS Humanitas Research Hospital that fulfill the above-mentioned inclusion and exclusion criteria with all the information they need to sign the informed consent. A signed copy of the informed consent will be collected.

10.1. Photon-Counting CT

Photon-Counting Computed Tomography (PCCT) will be performed using the Siemens Healthineers **NAEOTOM AlphaCT system**, which represents the latest advancement in CT imaging technology. This system is the first to utilize photon-counting detector (PCD) technology, which differs significantly from traditional energy-integrating detectors used in conventional CT systems. Unlike traditional CT detectors that measure the total energy deposited by x-ray photons, photon-counting detectors in the NAEOTOM Alpha system count each individual photon and measure its energy. This enables the system to differentiate between x-ray photons of different energy levels, providing true spectral imaging capability without the need for additional hardware or multiple acquisitions. The PCDs are made from Cadmium Telluride (CdTe), a semiconductor material that directly converts x-ray photons into electrical signals with high efficiency. CdTe detectors are known for their superior energy resolution and are less susceptible to electronic noise, which is crucial for maintaining high image quality at lower radiation doses.
The NAEOTOM Alpha offers ultra-high spatial resolution, achieving voxel sizes as small as 0.2 mm. This allows for detailed visualization of small anatomical structures, such as PGS and cartilage evaluation.. The system provides multi-energy imaging by detecting photons at different energy levels simultaneously.
This capability enables the generation of spectral images that can differentiate between materials based on their energy absorption characteristics. For example, it can distinguish between bone, soft tissue, and pathological tissues like laryngeal cancer.. The system's ability to separate photons by energy improves the contrast-to-noise ratio, especially in challenging imaging scenarios where different tissues or materials have similar attenuation properties at conventional energy levels. The advanced PCD technology reduces common CT artifacts such as beam hardening and metal artifacts. This results in clearer images, particularly in areas with high-density structures like the cortex of cartilage, where traditional CT systems might struggle. The NAEOTOM Alpha can achieve superior image quality with a lower radiation dose compared to traditional CT systems.

Imaging Protocol:

Contrast-enhanced PCCT imaging will be performed as per routine clinical practice. No changes in routine medical practice will be implementedThe system typically operates with adjustable kVp settings, ranging from 40 to 140 kVp, depending on the specific clinical requirements. Optimization of tube voltage will be performed based on clinical characteristics.
Axial scanning might be performed for accurate evaluation of larynx. supports multiple scan modes, including helical and axial scanning, tailored for specific clinical applications, such as high-resolution imaging of the head and neck.

10.2. IMAGING ANALYSIS

Images will be reviewed on a dedicated workstation (e.g., Syngo.via, Siemens Healthineers or MedStation) by three radiologists specializing in head and neck, two with more than 10 years of experience, and one with over 2 years of experience.

Image Evaluation:
The PGS invasion and cartilage involvement will be assessed using a predefined scoring system based on established criteria

PCCT evaluation

1. Paraglottic Space (PGS)

Score	Imaging Features	Interpretation
0	Normal fat planes, preserved symmetry, no effacement or abnormal enhancement	No PGS invasion
1	Mild asymmetry or effacement of paraglottic fat without discrete mass or enhancement	Indeterminate / suspected minimal invasion
2	Focal abnormal soft tissue in the PGS, partial fat replacement, moderate enhancement	Probable PGS invasion
3	Complete effacement of paraglottic fat, clear soft tissue mass, bulging into adjacent structures	Definite PGS invasion

2. Cartilage involment

Score	Imaging Features	Interpretation
0	Intact cortex, no signal change or demineralization, preserved cartilage contour	No cartilage invasion
1	Cortical irregularity or mild demineralization, without definite intrachondral extension	Indeterminate / early involvement
2	Focal intrachondral signal alteration or lysis (esp. inner cortex), partial thickness erosion	Probable cartilage invasion
3	Gross cartilage destruction, transcartilaginous extension, or invasion of both inner and outer cortex	Definite cartilage invasion

3. PCCT C

Total Score	Clinical Suggestion
0–1	Likely candidate for conservative treatment
2–3	Close evaluation needed; consider MRI confirmation
4–6	High risk for extensive invasion; consider open surgery or laryngectomy

Quality Assessment:
Image Quality: The overall quality of the images will be evaluated using a four-point Likert scale (1 = poor, 2 = average, 3 = good, 4 = excellent). This assessment will focus on PGS and cartilage involvement, the ability to differentiate between soft tissue and cartilage, and the presence of artifacts.

Quantitative Analysis:
For quantitative analysis, Hounsfield Units will be measured by placing circular small Regions of Interest (ROIs) on the identified tumor, surrounding PGS, and the adjacent cartilage in both PCCT.
Noise and Signal Analysis: An additional ROI will be placed in an area of air outside the neck to determine the background noise (N).
Signal-to-Noise Ratio (SNR): SNR will be determined for the soft tissue of the tumor and adjacent PGS and cartilage, using the equation:
SNR=Mean HU of tissueStandard deviation of noise (N)SNR=Standard deviation of noise (N)Mean HU of tissue
Contrast-to-Noise Ratio (CNR): CNR between tumor and surrounding PGS and cartilage will be calculate.

MRI evaluation

To compare MRI with Photon-Counting CT (PCCT) in the context OF t2-t3 laryngeal cancer , particularly focusing on PCCT's spectral capabilities, we will look at how both modalities can differentiate tumor from surrounding tissues (PGS and cartilage).
PCCT, with its spectral imaging capability, can differentiate between tissues based on their energy-dependent attenuation characteristics. By capturing multi-energy data, PCCT can create material-specific images, potentially allowing for the differentiation between tumor and surrounding inflamed tissue. Spectral imaging can be used to generate virtual non-contrast images, iodine maps (if contrast is used), and material decomposition images. The virtual non-contrast images can enhance soft tissue differentiation, while material decomposition techniques could theoretically help in distinguishing tumor from surrounding tissue.
We aim to compare the sensitivity and specificity of PCCT and MRI in detecting PGS invasion and cartilage involvement.This could be done by assessing how well each modality identifies these conditions against the gold standard of surgical findings.

Accuracy Assessment:

Surgical findings and histology will be used as the **gold standard** to determine the accuracy of each PCCT .

Sensitivy, specificity, PPV, NPV and accuracy:

Sensitivity: Proportion of true positives (correctly identified by imaging) among all cases confirmed surgically.

Specificity: Proportion of true negatives (correctly identified as not having the pathology by imaging) among all cases confirmed surgically.

Positive Predictive Value (PPV): Proportion of positive imaging results that are true positives.

Negative Predictive Value (NPV): Proportion of negative imaging results that are true negatives.

11. SAFETY ASSESSMENT AND REPORTING

11.1. Safety assessment and reporting

Considering the nature of the observational prospective that will not imply any modification in clinical practice, no AEs is expected.

12. STATISTICAL CONSIDERATIONS

12.1. Sample size

This Pilot study will involve sixty patients. Descriptive statistics will be taken into consideration for comparison purposes and for hypothesis assessment.

A Shapiro-Wilk test will be conducted to assess the normality of data distribution, with a significance level set at 0.05. Given the pilot and observational nature of the study, no non-inferiority or superiority hypotheses will be tested, and analyses will focus on descriptive and comparative statistics with post-hoc statistical analysis on imaging quality and accuracy. Data from previousstudy will be taken into consideration.

To reduce the risk of Type I errors in multiple comparisons, Bonferroni correction will be applied where necessary.

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Descriptive statistics will be used to summarize quantitative variables, reporting means and standard deviations for normally distributed data or medians and interquartile ranges for non-normally distributed data. For categorical variables, frequencies and percentages will be calculated. The diagnostic accuracy of Photon-Counting CT (PCCT) and MRI will be assessed using sensitivity, specificity, PPV, and NPV. Surgical findings, when applicable and available, will serve as the gold standard for these comparisons. Significance threshold will be p value < 0.05 (adjusted with Bonferroni when needed)

Post-hoc statistical analysis:
Receiver Operating Characteristic (ROC) curves will be generated for each imaging modality to evaluate diagnostic performance, with the Area Under the Curve (AUC) providing a summary measure of accuracy.
McNemar's test will be employed to compare sensitivity and specificity between PCCT and MRI, especially when the same patients are evaluated across different modalities.
Intraclass Correlation Coefficient (ICC) will be calculated to assess inter-rater reliability among the three radiologists evaluating the imaging data.
Quantitative Analysis: For both PCCT, Hounsfield Units (HU) will be measured by placing Regions of Interest (ROIs) on identified lesions and surrounding tissues. Signal-to-Noise Ratio (SNR) will be calculated using the formula
SNR=Mean HU of tissue Standard deviation of noise(N)
SNR = \frac{Mean \, HU \, of \, tissue}{Standard \, deviation \, of \, noise (N)}SNR=Standarddeviationofnoise(N)MeanHUoftissue.

Contrast-to-Noise Ratio (CNR) will be determined for tumor versus surrounding tissue using the formula:

The results of this prospective observational study, focusing on PCCT, will be compared with retrospective data from patients who previously underwent SECT at our Center. This comparison will aim to evaluate the relative diagnostic accuracy, sensitivity, specificity, and overall effectiveness of PCCT. Previous CT scan data obtained from the same cohort provides a historical control, allowing for a direct assessment of the potential advancements that PCCT may offer in the diagnosis and management of otologic conditions.

12.2. Analysis.

Statistical methods will include the following or equivalent:
Shapiro-Wilk Test: To assess the normality of data distribution.
Bonferroni Correction: To adjust for multiple comparisons and reduce the risk of Type I errors.
Descriptive Statistics: Summarizing means, standard deviations, medians, interquartile ranges, frequencies, and percentages for the study population.
Contingency Tables: For calculating sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of each imaging modality.
Receiver Operating Characteristic (ROC) Curves: To evaluate diagnostic performance and calculate the Area Under the Curve (AUC).
McNemar's Test: To compare the sensitivity and specificity between different imaging modalities in paired data.
Intraclass Correlation Coefficient (ICC): To assess inter-rater reliability among the radiologists.
Paired t-tests or Wilcoxon Signed-Rank Tests: For comparing quantitative imaging metrics like Signal-to-Noise Ratio (SNR) and Contrast-to-Noise Ratio (CNR) between imaging modalities.

Bland-Altman Analysis: To evaluate the agreement between different imaging modalities regarding

Propensity Score Matching: For matching cohorts in the prospective and retrospective study to control for confounding variables.

Subgroup Analysis: Sensitivity analysis to assess the robustness of the results across different subgroups.

13. QUALITY ASSURANCE AND CONTROL

Quality Assurance and Quality Control systems based on written SOPs are in place at the Sponsor site.

13.1. Data handling and record keeping / archiving

The investigator must keep the documents on file for at least 7 years after completion or discontinuation of the study. After that period, the documents may be destroyed, subject to local regulations. Before proceeding to documents' destruction, sites must inform the Coordinating Investigator/delegate in writing. Should the investigator wish to assign the study records to another party or move them to another location, the Coordinating Investigator/delegate must be notified in advance.

13.2. Case Report Forms

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code. The Informed Consent Form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee, and the regulatory authorities to have direct access to source data which supports the data on the e-CRF (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel bound by professional secrecy, must keep confidential all personal identity or personal medical information (according to confidentiality rules). The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

13.3. Source documents

Source data must be available at the site to document the existence of the study participants. Source data include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

14. CONFIDENTIALITY OF PATIENT RECORDS

The investigator assures that patients' anonymity should be maintained and that their identities are protected from unauthorized parties. Particular attention should be paid whenever patient data are supplied to third parties and may be autonomously processed.

The investigator should keep in a confidential way a patient identification log recording both patient code and name. The investigator should also maintain patients' written consent forms, in strict confidence (i.e. not for submission to the Coordinating Investigator).

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

15. ETHICAL CONSIDERATIONS

The responsible investigator ensures that this study is conducted in agreement with this protocol, the Good Clinical Practice, the current version of Declaration of Helsinki and the applicable regulations.

The protocol and any amendments are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

16. INFORMED CONSENT

All patients should be informed of the aims of the study. They should be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.
It should be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This does not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before any study related procedure is performed. The written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the Investigator who has provided the study information.

17. DATA OWNERSHIP

Humantias University , Promoter of the study is the owner of the data resulting from the study. All centers and investigators participating in the study should be made aware of such circumstance and not to disseminate information or data without the prior written consent by Humantias University.

18. PUBLICATION POLICY

After completion of the study, the Coordinating Investigator prepares a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript is delivered to the co-authors for comments and then sent to a scientific journal for publication.

All publications, abstracts, presentations, manuscripts and slides - issued by the Investigators of the collaborative sites and including data from the present study- should be submitted to and reviewed by the Coordinator Investigator at least 3 (three) weeks in advance the planned date for the submission to the scientific journal.

19. FUNDING AND SUPPORT

Funding for the study will be provided by ANTHEM.

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