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REVIEW

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Quantitative measurements of radiation-induced fibrosis for head and neck cancer: A narrative review

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Abstract

Objectives: To provide a comprehensive summary of the different modalities available to measure soft tissue fibrosis after radiotherapy in head and neck cancer patients.

Data Sources: PubMed, Scopus, and Web of Sciences.

Review Methods: A search was conducted using a list of medical subject headings and terms related to head and neck oncology, radiation fibrosis, and quantitative measurements, including bioimpedance, MRI, and ultrasound. Original research related to quantitative measurement of neck fibrosis post-radiotherapy was included without time constraints, while reviews, case reports, non-English texts, and inaccessible studies were excluded. Discrepancies during the review were resolved by discussing with the senior author until consensus was reached.

Results: A total of 284 articles were identified and underwent title and abstract screening. Seventeen articles had met our criteria for full-text review based on relevance, of which nine had met our inclusion criteria. Young's modulus (YM) and viscoelasticity measures have demonstrated efficacy in quantifying neck fibrosis, with fibrotic tissues displaying significantly higher YM values and altered viscoelastic properties such as increased stiffness rate-sensitivity and prolonged stress-relaxation post-radiation. Intravoxel incoherent motion offers detailed insights into tissue changes by assessing the diffusion of water molecules and blood perfusion, thereby differentiating fibrosed from healthy tissues. Shear wave elastography has proven to be an effective technique for quantifying radiation-induced fibrosis in the head and neck region by measuring shear wave velocity.

Conclusion: There are various modalities to measure radiation-induced fibrosis, each with its unique strengths and limitations. Providers should be aware of these implications and decide on methodologies based on their specific clinical workflow.

Level of Evidence: Step 5.

KEYWORDS
acoustic radiation force impulse, indentation, radiation-induced fibrosis, shear wave elastography, viscoelasticity, Young's modulus

1 | INTRODUCTION

Radiation therapy (RT), used as either definitive or adjuvant treatment, is widely used to treat patients with head and neck squamous cell carcinoma (HNSCC).[1,2] While effective, RT often leads to toxicity, including chronic xerostomia, neck pain, dysphagia, and radiation-induced fibrosis (RIF).[3–7] RIF is thought to result from continuous inflammation in the muscles and soft tissues near the treatment site, disrupting the healing process and leading to fibrosis.[8,9] Fibrosis of neck muscles and vasculature has been associated with lymphedema, dysphagia, impaired tongue function, and trismus, all of which significantly impact a patient's post-operative quality-of-life.[10] Therefore, the adoption of a noninvasive method to monitor progression of RIF after RT is necessary, as biopsy remains the current gold standard for diagnosing and quantifying RIF.

There are several quantitative methodologies to measure neck fibrosis, including indentation, suction, MRI, and ultrasound. Shear-wave elastography (SWE), an ultrasound technique, maps the elastic properties and stiffness of soft tissue, which can help identify or quantify progression of diseases associated with increased tissue stiffness. SWE utilizes acoustic radiation force imaging (ARFI) to create shear waves that travel perpendicular to the ultrasound beam. The velocity of these waves directly correlates with tissue stiffness, offering a quantitative assessment of fibrosis.[11–14] Existing literature has successfully applied SWE for the detection and classification of fibrosis in various organ systems, including the liver,[15] breast,[16] and kidney.[17]

Despite preliminary studies investigating different quantitative measurements for RIF in patients after head and neck RT, there is no recent comprehensive summary of all the modalities available to measure fibrosis post-radiotherapy in this population. This article details quantitative methodologies of measuring RIF in head and neck oncology, with emphasis on SWE, and describes how otolaryngologists can adopt these methods to monitor RIF throughout and after patients are treated for head and neck cancer.

2 | METHODS

Our aim was to review the different modalities available to quantitatively measure RIF in head and neck cancer survivors, focusing on SWE. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines in performing this study.

2.1 | Search strategy

A search strategy was developed by R.A. and P.J, an experienced health-science librarian at the University of Kansas Medical School, and reviewed by the senior author, A.M.B. Three comprehensive databases (PubMed, Scopus, and Web of Sciences) were searched on August 10th, 2023 with no date range exclusion. Queries were formulated using medical subject headings (MeSH) and search terms pertaining to head and neck oncology, radiation fibrosis, and quantitative measurements, including bioimpedance, MRI, and ultrasound. Relevant articles' MeSH terms and keywords were extracted and integrated into subsequent searches until all applicable terms were captured. Table 1 outlines the complete search criteria and outcomes for each database. Articles were then uploaded to the web-based application Covidence to facilitate title and abstract screening.[18] This software automatically removed duplicates prior to screening and full-text review. Additionally, references from review articles were checked to further identify eligible studies.

2.2 | Inclusion and exclusion criteria

We conducted a comprehensive review of studies that utilized quantitative methods to measure post-radiation fibrosis in the head and neck region. Our criteria were inclusive of original investigations without any time restrictions. We omitted review articles, case reports, studies not in English, studies without access to full texts, and articles that were unrelated or did not directly measure fibrosis. The initial screening of titles and abstracts was completed by R.A. and A.B. All potentially relevant articles, including those without abstracts, underwent full-text review. In cases of uncertainty or disagreement, we sought the opinion of the senior author (A.M.B.) and discussed until consensus was reached.

3 | RESULTS

3.1 | Search results

A total of 280 studies were initially identified, of which 22 were duplicates. An additional four studies were included through a review of references of review articles.[19] Following title and abstract screening, 245 studies were deemed irrelevant, narrowing the selection to 17 studies for full-text review. A total of 9 articles were included in this narrative review after excluding studies not focused on quantitative measurements of fibrosis (3), review articles (2), case reports (1), studies lacking full text (1), and those not in English (1) (Supplementary 1). A summary of each study including the author and year, quantitative measure utilized, property measured, and main findings are described in Table 2.

3.2 | Indentation measured by Young modulus

Two studies highlighted the use of Young's modulus (YM), a quantitative measure of a material's deformability defined as the ratio of applied force to the resulting deformation, for head and neck fibrosis. In the context of assessing tissue indentation, YM is calculated based on the pressure applied and the corresponding indentation (Figure 1).[20] Zheng and colleagues conducted a feasibility study using an ultrasound palpation system that incorporates YM to measure neck

TABLE 1 Search criteria and results.

PubMed Search #1	("Elasticity Imaging Techniques"[mh] OR "acoustic radiation force impulse imaging"[tw] OR "arfi imaging"[tw] OR "arfi imagings"[tw] OR "elasticity imaging technique*"[tw] OR "elastogram*"[tw] OR "elastograph*"[tw] OR "magnetic resonance elastograph*"[tw] OR "sonoelastograph*"[tw] OR "tissue elasticity imaging"[tw] OR "tissue elasticity imagings"[tw] OR "vibro acoustograph*"[tw])	17,325
PubMed Search #2	("radiation-induced fibros*" [tw] OR "RIF" [tw] OR "Radiation Fibrosis Syndrome"[Mesh] OR "radiation fibros*" [tw] OR ("Fibrosis"[Mesh] AND ("radiation" [tw] OR "radiation injuries" [mh])))	10,625
PubMed Search #3	("Radiotherapy"[Mesh] OR "radiotherap*" [tw] OR "radiation therap*" [tw] OR "Head and Neck Neoplasms/ radiotherapy"[Mesh])	442,273
PubMed Search #4	("Head and Neck Neoplasms"[Mesh] OR "head and neck cancer*"[tw] OR "head and neck neoplasm*"[tw])	360,283
PubMed Search #5	"Electric Impedance"[MeSH] OR "electric impedance" [tw] OR "electrical impedance" [tw] OR "bioimpedance" [tw] OR "dielectric measurements" [tw] OR "Mechanical Phenomena" [MeSH] OR "Magnetic Phenomena" [MeSH] OR "Suction/methods" [MeSH] OR "Suction" [tw]	1,445,215
PubMed Final	#1 AND #2 AND #3 AND #5	156
Scopus	TITLE-ABS-KEY ("head and neck neoplasms" OR "head and neck cancer") AND TITLE-ABS-KEY ("Radiotherapy" OR "radiation therapy") AND TITLE-ABS-KEY ("elasticity imaging technique" OR "elastography" OR "elastogram" OR "elastograph" OR "sonoelastograph" OR "tissue elasticity imaging" OR "electric impedance" OR "electrical impedance" OR "bioimpedance" OR "dielectric measurements" OR "ballistometry" OR "mechanical phenomena" OR "magnetic phenomena" OR "suction")	66
Clarivate	(ALL = (Otolaryngology) OR ALL = (Head and Neck Neoplasm) OR ALL = (Head and Neck Cancer) OR ALL = (Ear, Nose, and Throat) OR ALL = (Ear, Nose, Throat)) AND (ALL = (Elastography) OR ALL = (elasticity imaging technqiues) OR ALL = (elastograph) OR ALL = (sonoelastography) OR ALL = (tissue elasticity imaging) OR ALL = (electrical impedance) OR ALL = (electric impedance) OR ALL = (bioimpedance) OR ALL = (dielectric measurements) OR ALL = (suction) OR ALL = (mechanical phenomena) OR ALL = (magnetic phenomena)) AND (ALL = (radiotherapy) OR ALL = (radiation fibrosis) OR ALL = (radiation-induced fibrosis) OR ALL = (fibrosis))	58
Review of References		4
Total		284

tissue fibrosis in 8 normal and 4 irradiated patients. Their findings demonstrated that YM in confirmed fibrotic neck tissues is up to eight times higher than in normal subjects. A subsequent study by the same authors used YM to measure post-irradiation neck fibrosis in 105 patients and correlated it with conventional measurement methods, such as grading levels of fibrosis through hand palpation and neck rotation testing.[21,22]

3.3 | Indentation measured by viscoelasticity

Indentation measured by Viscoelasticity operates similarly to YM, as it involves applying force and recording indentation measurements, but focuses on characteristics of soft tissue mechanics such as stiffness rate-sensitivity and stress-relaxation.[23,24] Stiffness rate-sensitivity quantifies how swiftly tissue stiffens upon applying force, whereas stress-relaxation measures the time required for stressed tissue to relax after removing force.[25,26] Several studies outside the head and neck literature use YM to quantify indentation but neglect the inherently nonlinear and time-dependent stress–strain relationship of biological tissues. This time-dependent behavior is referred to as viscoelasticity. In viscoelastic behavior, tissue exhibits a specific deformation and recovery pattern, depending on the rate of force application and removal.[27] Therefore, a rapid application of force induces greater deformation, and swift removal expedites recovery to equilibrium, and vice versa. Post-radiation, there are changes in this nonlinear and viscoelastic behavior, attributable to systemic alterations in tissue components, like collagen and water.[24,28] By comparing these altered physical properties, clinicians can differentiate between normal and irradiated tissues.

Huang et al. developed a viscoelastic model to evaluate fibrosis in the neck region following radiation. They noted that tissue with increased fibrosis displayed a more rapid increase in stiffness when pressure was applied, compared to healthy normal tissue. Furthermore, the irradiated and fibrosed tissue took a longer time to relax after indentation and did so to a lesser extent. These observations demonstrate that the characteristics of indentation and viscoelasticity can serve as parameters to differentiate between varying degrees of fibrosis.[29]

3.4 | Imaging

Imaging techniques, such as magnetic resonance imaging (MRI), have been used to differentiate healthy from fibrosed tissues.[30] Traditional diffusion-weighted imaging (DWI), a type of MRI, evaluates water diffusion through tissues, which is limited by their interactions with intracellular organelles, and thus dependent on tissue cellularity.

TABLE 2 Summary of included articles.

Author, year	Quantitative method	Property measured	Findings
Zheng, 2000[21]	Young's modulus	Young's modulus (kilopascals; kPa)	Young's modulus was significantly greater in irradiated tissues compared to normal. There was limited variation among multiple neck sites, inter-rater, and intra-rater measurements
Leung, 2002[22]	Young's modulus	Young's modulus (kPa)	Young's modulus is a showed a significant positive correlation with hand palpation scores and a significant negative correlation with neck rotation for patients who received prior neck radiation
Huang, 2005[29]	Indentation and viscoelasticity	Young's modulus (kPa), Viscosity (seconds)	Patients in control cohort has significantly lower measurements of Young Modulus, shorter time to recover to equilibrium after indentation, and lower viscosity, indicating that the normal tissue relaxed to greater extent when compared to irradiated tissue. Irradiated tissue was associated with a larger initial stiffness and a faster increase in stiffness under loading
Badea, 2013[35]	Shear wave elastography (SWE)	Shear wave velocity (SWV, m/s)	Patients in the radiation therapy cohort had significantly greater average SWV compared to controls when measuring submandibular gland stiffness, indicating a structural change in the gland after radiation
Lai, 2013[33]	Intravoxel incoherent motion MR imaging (IVIM)	Pure diffusion, perfusion fraction, and pesudodiffusion coefficient	Pure diffusion and Perfusion fractions were significantly greater, while the pseudodiffusion coefficient was significantly lower, for post-chemoradiation fibrosis compared to nasopharyngeal cancer on MRI, suggesting these IVIM parameters are helpful in discriminating between the two
Kałużny, 2014[45]	Sonoelastography	Elasticity (kPa)	The elastography elasticity values were significantly greater in the radiation cohort for both the submandibular and parotid glands compared to nonradiated controls
Badea, 2015[36]	Shear wave elastography	Shear wave velocity (m/s)	Patients in radiation therapy cohort had significantly greater average SWV compared to controls when measuring parotid gland stiffness, indicating a structural change in the gland after radiation
Liu, 2015[46]	Shear wave elastography	Elasticity (kPa)	SWE stiffness measurements of deep and subcutaneous tissues were significantly greater in irradiated patients compared to age- and sex-matched controls
Wen, 2019[47]	Shear wave elastography	Elasticity (kPa)	The elasticity indices were increasing with greater duration post-irradiation. At 18 months, there was a significant increase in elasticity indices in the irradiated cohort compared to controls

Pathologic states, such as cancer and early stages of fibrosis, contain a greater number of intact cell walls than healthy tissue, resulting in more restricted water molecule movement. In DWI, unrestricted water molecules in healthy tissues undergo a phase shift, resulting in decreased intensity of the measured magnetic resonance (MR) signal. Conversely, restricted water molecules in pathologic tissues remain phase-stable, producing a hyperintense MR signal.[31] In contrast, intravoxel incoherent motion (IVIM) imaging differentiates between diffusion (the random motion of water molecules in tissue) and perfusion (the movement of blood in capillaries) in tissues. A bi-exponential MR signal decay indicates the presence of both diffusion and perfusion, while a mono-exponential decay suggests diffusion alone, typically found in fibrosed tissue.[32] Using this framework, Lai et al. observed that nasopharyngeal carcinoma (NPC) decayed bi-exponentially, reflecting its capillary network enabling both diffusion and perfusion, whereas fibrotic tissue decayed mono-exponentially, indicating distinct IVIM characteristics for each condition (Figures 2 and 3).[33]

3.5 | Acoustic radiation force imaging and shear wave elastography

Shear wave elastography (SWE) is an ultrasound technique used to assess tissue stiffness through the propagation of shear waves. SWE utilizes ARFI, which creates brief, high-intensity acoustic pulses to induce tissue deformation within a region of interest. The degree and speed of the tissue's response to this deformation are then monitored by ultrasound tracking beams. By analyzing the deformation wavefront at multiple points and correlating the measurements with the time elapsed, the shear wave velocity (SWV, m/s) can be determined.[34–36] The velocity of these waves correlates with the tissue's stiffness; the waves travel faster in stiffer tissues and slower in softer ones. The different SWVs are mapped onto an elastogram, which can then be used to estimate the stiffness at the region of interest.[37,38] Since majority of ultrasound machines use ARFI pulses to perform SWE, ARFI, and SWE have been used interchangeably in the literature.

ARFI has various medical applications, including the assessment of liver fibrosis, differentiation between benign and malignant breast lesions, measurement of cardiac stiffness, and characterization of carotid atherosclerosis.[39–42] In the head and neck region, ARFI has been able to differentiate between benign and malignant thyroid nodules.[43,44] More recently, it has been used to characterize tissue stiffness in the submandibular gland (SMG) and parotid gland (PG) following RT (Figures 4 and 5).[35,36] These articles demonstrated ARFI's ability to detect differences between irradiated and healthy salivary glands by calculating distinct SWVs for each tissue type. Similarly, three additional studies investigated the utility of SWE for noninvasively measuring RIF in the head and neck region. Kalunzy et al. noted significantly greater elastography values in 52 irradiated salivary glands compared to 54 nonirradiated controls.[45] Liu et al. observed increased stiffness measurements of the sternocleidomastoid (SCM) and overlying subcutaneous tissue in a cohort of 25 irradiated patients compared to 25 controls, noting a significant association between increased stiffness and time elapsed since RT.[46] Wen etal. further substantiated these findings in a study involving 53 patients with NPC. They observed a statistically significant increase in elasticity indices of the SCM measured 18 months after radiotherapy compared to before.[47] Collectively, these studies indicate ARFI and SWE can be a non-invasive modality for quantifying RIF following head and neck radiotherapy.

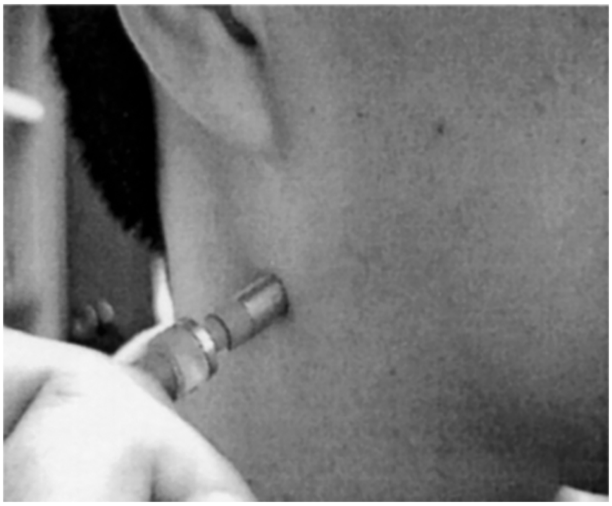

FIGURE 1 Indentation for Young's modulus and visoelasticity. Patient being tested with ultrasound probe to measure Young's modulus and viscoleasticity. Figure was adapted with permission.[21]

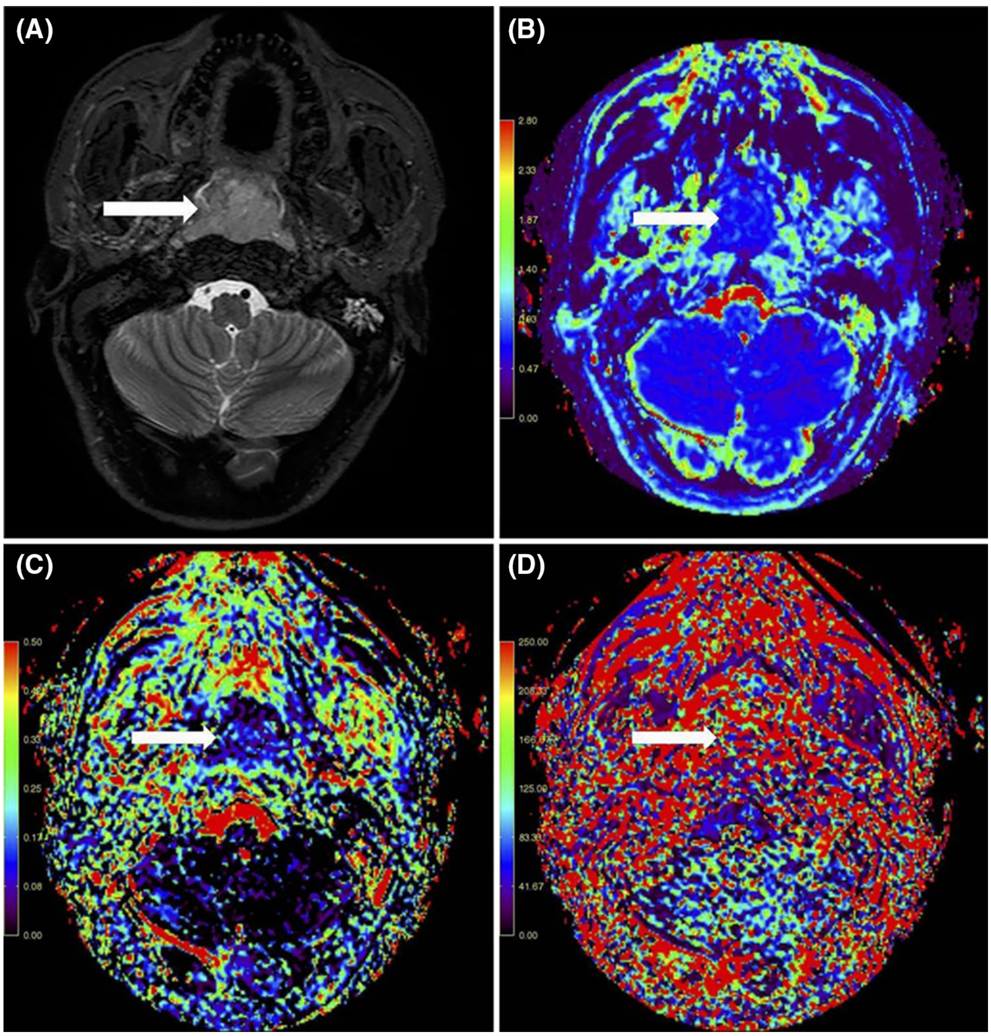

FIGURE 2 Intracoherent intravoxel imaging (IVIM) of Nasopharyngeal Carcinoma (NPC). A 47-year-old man with newly diagnosed NPC illustrating IVIM parameters: (A) axial T2-weighted image showing bulky hyperintense nasopharyngeal tumor (arrow); (B) diffusion (*D*) map showing reduced *D* value ($0.675 \pm 0.124 \times 10^{-3}$ mm^2/s); (C) perfusion fraction (*f*) map demonstrating reduced *f* value (0.106 ± 0.0070); (D) pseudodiffusion coefficient (*D**) map showing increased *D** value ($101.904 \pm 67.231 \times 10^{-3}$ mm^2/s). Figure and caption were used with permission.[33]

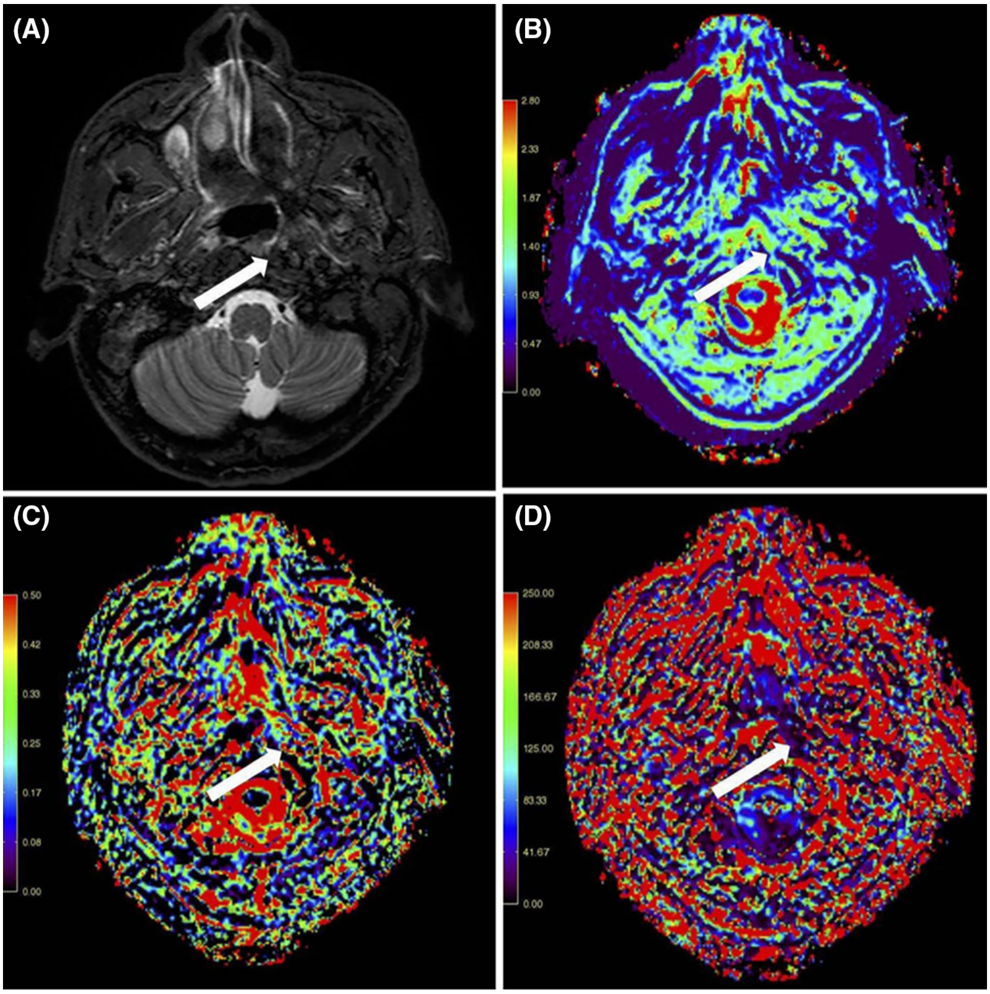

FIGURE 3 Intracoherent intravoxel imaging of post-chemoradiation fibrosis. A 54-year old man with post-chemoradiation fibrosis with characteristic changes in IVIM parameters: (A) axial T2-weighted image showing a heterogenous hyperintense soft tissue lesion on the left side of the nasopharynx (*arrow*); (B) diffusion (*D*) map showing increased *D* value ($1.391 \pm 0.445 \times 10^{-3}$ mm^2/s); (C) perfusion fraction (*f*) map demonstrating elevated *f* value (0.167 ± 0.114); (D) pseudodiffusion coefficient (D^*) map showing reduced D^* value ($88.001 \pm 70.518 \times 10^{-3}$ mm^2/s). Figure and caption were used with permission.[33]

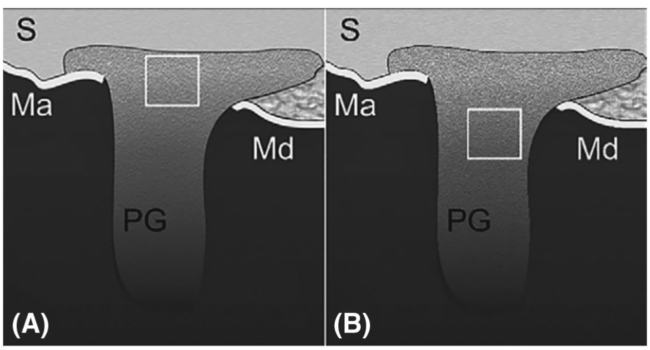

FIGURE 4 Acoustic radiation force impulse (ARFI) imaging to measure radiation fibrosis. The figure illustrates the transverse US plane and place of the region of interest (ROI). (A) ROI at subcapsular parenchyma, (B) ROI at central parenchyma. White box—ROI, PG—parotid gland, Ma—mastoid, Md—mandible ramus, S—skin and subcutaneous fat. The figure and caption were adapted with permission.[36]

4 | DISCUSSION

This article reviews different techniques of quantifying RIF following radiotherapy for head and neck cancer. YM and indentation with visco-elasticity are reliable quantification methods taking into account the innate characteristics of skin, while imaging modalities like IVIM provide a more detailed analysis of tissue at the molecular. Finally, acoustic radiation force impulse (ARFI) imaging and SWE allow for simple and accessible measurement of stiffness in the head and neck region.

4.1 | Advantages and limitations

YM's applicability in a clinical setting. First, Zheng et al.'s study had variations in measurements of ±7% taken 1 week apart, indicating that YM is reliable for monitoring changes in neck tissue after radiotherapy.[21] Similarly, their subsequent study emphasized YM's increased sensitivity to subtle changes in amount of fibrosis and correlation with radiation dose levels.[22] Despite these captivating benefits, the biggest limitation of using YM is its stringent requirement for a standardized manner of measuring fibrosis across different sites, a critical factor for accurate interpatient and intra-patient comparisons. However, this requirement for site-specific consistency can be turned into an advantage, as it allows for precise discrimination of tissue stiffness at various subsites in the neck. This precision could potentially lead to the creation of detailed fibrosis maps to aid in early detection of fibrotic changes and prompt interventions to slow fibrosis.[22]

Indentation with viscoelasticity has similar advantages as YM, due to the same operational technique between the two methods. Its

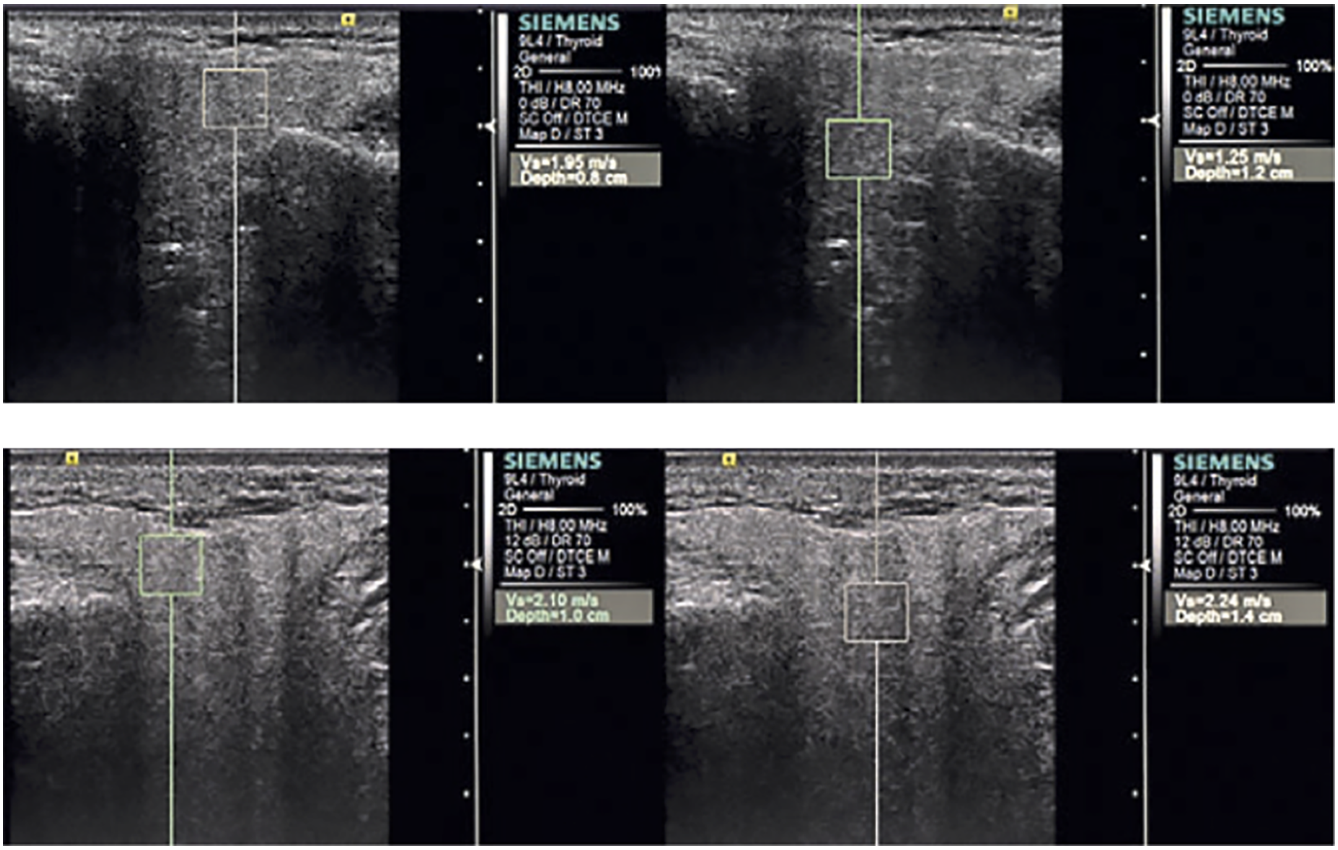

FIGURE 5 Acoustic radiation force impulse imaging of parotid gland. ARFI imaging of the left parotid gland in a 37-year-old healthy patient (top) and a 56-year-old patient who underwent radiotherapy (bottom). The figures and caption were adapted with permission.[36]

primary benefit lies in accounting for the physical properties of tissues, but this also presents a significant challenge. On top of the same limitations as YM, creating a system to accurately measure the viscoelastic properties of tissue is mathematically complex and needs to be individualized per patient given each patient's unique skin characteristics, limiting its clinical utility.[29]

Imaging modalities have also proven to be effective in quantifying RIF. IVIM imaging excels in diagnosing fibrosis by differentiating molecular diffusion from microcirculation using the bi-exponential model, which enables it to stage fibrosis early and accurately.[48] This outperforms other noninvasive methods by providing a more detailed quantification for differentiation between RIF and normal tissue. Despite its effectiveness, IVIM has notable drawbacks. First, it is time-consuming, with scans taking anywhere from 30 min to over an hour and requiring patients to schedule appointments, potentially leading to extended waiting periods. Additionally, the substantial cost of IVIM may limit its accessibility, particularly when compared to other, less expensive modalities discussed in this article.

Ultrasound techniques like SWE and ARFI allow for real-time measurements to monitor progression of fibrosis, but have certain disadvantages. Both ARFI and SWE provide objective quantification of tissue stiffness, but their comparability across different commercial ultrasound systems is limited by several factors. Different ultrasound probes and their frequencies can affect the generation and detection of shear waves. High-frequency probes are often better for superficial tissues, while lower frequencies are preferred for deeper tissues. Therefore, the choice of probe may impact the measurement of SWV and estimation of tissue stiffness.[49] Ultrasound-specific software and algorithms used to analyze the shear wave data can vary between ultrasound systems. These differences can lead to variability in how SWV is calculated, potentially affecting the reproducibility and comparability of results across different machines.[50] In addition, operator experience and technique can further introduce variability, as consistent placement of the probe and appropriate pressure application are crucial for reliable measurements. Variations in these factors can lead to differences in shear wave generation and propagation, affecting the resulting SWV. Moreover, the absence of standardized reporting guidelines can also lead to variability in how results are communicated and compared across different ultrasound systems.

Another major limiting factor of SWE and ARFI is anisotropy. For SWE, the tissue of interest is assumed to be isotropic (physical property that has the same value when measured in different directions), however, skeletal muscle is inherently anisotropic. Therefore, the induced ARFI pulses propagate faster when parallel to the skeletal muscle fibers and slower when perpendicular to the same fibers.[51] This limits the clinical utility of SWE measurements of skeletal tissue, but it can still be used to quantify fibrosis of soft tissue, such as salivary glands. Furthermore, protocol inconsistencies like the size, shape, and position of the region of interest on the elastogram can further affect the results, thereby not providing entirely precise elastography indices.[38] Environmental factors, such as room temperature and patient positioning, can influence measurements, albeit to a lesser extent.[52]

4.2 | Implications for clinical practice

In the context of clinical utility, SWE and ARFI are the only techniques to have undergone clinical trial evaluation for fibrosis measurement. One prospective study enrolled children with hepatobiliary diseases and demonstrated a significant correlation between SWE values and the extent of liver fibrosis as determined by biopsy results.[53] Similarly, a multi-institutional study assessing the accuracy of SWE found it to be more precise than aminotransferase platelet ratio index for grading liver fibrosis.[54] To our knowledge, there have been no clinical trials involving SWE within the field of Otolaryngology-Head and Neck Surgery. At our institution, we have carried out a preliminary study investigating quantifying radiation-induced neck fibrosis in patients post-head and neck radiotherapy using SWE. Our findings indicate that patients with HNSCC experience increased stiffness in the SCM, both ipsilaterally and contralaterally, compared with age and gender-matched controls who did not receive radiotherapy. Although our pilot study was limited to 20 patients, the results suggest that SWE may serve as a valuable instrument for tracking fibrosis progression during a patient's treatment, potentially facilitating early interventions that could enhance the patient's quality of life.

It is also essential to recognize the correlation between the degree of fibrosis and the methodologies that exhibit high specificity for differentiating fibrosis stages, which may aid early interventions. YM has been noted to correlate positively with the radiation dose, specifically in a study where patients who received an intensified radiation dose on one side of the neck demonstrated higher YM values than the non-boosted contralateral side.[22] Although indentation and viscoelastic measurements have not been explicitly examined for correlation with radiation dose, it can be inferred that, given YM's reliance on indentation, a similar relationship may exist. From an imaging perspective, IVIM distinguishes between pathologies through distinct diffusion and perfusion values that are subsequently contrasted with those of other tissues. Considering that IVIM relies on tissue cellularity, it can be postulated that the initial stages of fibrosis would result in different diffusion and perfusion values relative to more advanced stages, as tissue cellularity changes throughout the development of fibrosis. This specificity emphasizes its potential utility in correlating different degrees of fibrosis. Moreover, ultrasound techniques (ARFI/SWE) have also been found to identify varying fibrosis levels. Wen et al. conducted SWE assessments at multiple intervals surrounding radiotherapy and observed a progressive increase in tissue stiffness from before radiotherapy to 1.5 years after treatment, suggesting that SWE can detect the evolution of fibrosis as it progresses in patients.[47]

To our knowledge, there have been no studies measuring the effectiveness of interventions for RIF in the head and neck region using any of the quantitative measurements discussed in this article. Majority of studies assessing head and neck radiation side effects focus on mucositis and trismus, which are monitored using patient-reported outcomes and the dental gap, respectively.[55,56] One study did use US imaging to quantify the fibrotic depth, facilitating the calculation of fibrotic volume within a specified region in a randomized clinical trial assessing the efficacy of pentoxifylline and tocopherol for reducing superficial RIF.[57] US was used to track the change in fibrotic depth longitudinally throughout the study duration. At the end of the study, there was a statistically significant difference between the control and treatment arms, suggesting US can be utilized to measure the effectiveness of interventions. Although SWE measurements were not incorporated, SWE's utility can be extrapolated from the success of US given that SWE is an US technique.

Each methodology assessed exhibits unique strengths to monitor head and neck RIF, but SWE/ARFI seems to be the most clinically pragmatic option. SWE provides a robust, accessible, and cost-effective method for the evaluation of RIF in the head and neck region. Its capability to non-invasively capture the temporal development of fibrosis offers a significant advantage for continuous patient monitoring. Moreover, the noninvasive nature of SWE, coupled with its ability to offer immediate results, aligns well with the clinical workflow. Though SWE's clinical utility has not been validated in Otolaryngology yet, it may be promising tool for early intervention and potentially improving the quality of life for patients undergoing radiotherapy.

5 | CONCLUSION

The evaluation and management of RIF in patients who have undergone head and neck radiotherapy is necessary to optimize early interventions to minimize side effects of RIF, such as lymphedema, dysphagia, tongue function, and trismus. This review provides a comprehensive summary of multiple diagnostic modalities—YM, indentation and viscoelasticity, MRI, and ARFI/SWE—each offering unique advantages and limitations. YM and viscoelasticity parameters offer high precision but necessitate significant resources to accurately collect stiffness values. Similarly, MRI techniques like IVIM offer highly specific measurements but are limited due to accessibility and time constraints. The ultrasound techniques, ARFI and SWE, are non-invasive methods with promising utility; however, further studies controlling for anisotropy and standardization across different ultrasound systems are necessary for clinical applicability.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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