ISSN (Print) 1226-1750
ISSN (Online) 2233-6656
Journal of Magnetics 25(1), 110-116 (2020) https://doi.org/10.4283/JMAG.2020.25.1.110

Radiomics in Oncology: Method and Clinical Applications

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(Received 18 February 2019, Received in final form 4 March 2020, Accepted 5 March 2020)

Radiomics is a field for quantitative image assessment and research using a variety of sophisticated and complex algorithms by extracting a significant and numerous amount of specific functional elements (called texture feature) from medical images. It is mainly used in oncology and can provide a variety of capabilities in a non-invasive way, such as explaining the tumor phenotype, monitoring the response to treatment, comparing with normal tissue, diagnosing the prognosis of the patient and predicting survival. In this study, we will introduce of the workflow of radiomics and discuss the types of texture features, application of clinical cases, and the prospects of radiomics.

Keywords : radiomics, medical image, magnetic resonance imaging, fMRI, oncology, diagnostic markers

1. Introduction

Tumors that are biologically complex and have various growth specificities heterogeneous genetic phenotypes between different tumors and even within same type of tumors [1]. In general, cancer research has been carried out through research and diagnosis such as histopathological cell type analysis from a large number of patients and clinical or genetic data analysis based on long-periods collected data [2-4].

However, the study and analysis of tumors through these method is characterized by the growth of tumor cell mutations during tumor evolution, the lack of understanding of tumor heterogeneity and personal environment in each patient, and the dependence of subjective opinion on tissue diagnosis, clearly. Therefore, the possibility of objective and quantitative analysis is necessary. In addition, with the development of computer image processing and the improvement of the quality of the quality of medical images, the development of protocols for the image acquisition process has increased the possibility and expectation for image research. In modern social medical fields, medical images, such as computed tomography (CT), positron emission tomography (PET), or magnetic resonance (MR, mainly used T1, T2 and fmri) images are important factors in the stage of diagnosis, prevention, and treatment of tumors [5-7].

Quantitative features extraction and measurement using medical images can replace tissue biopsies, observations through surgical incisions, and minimizes the genetic heterogeneity of structures, non-invasively [8, 9]. Also, the extraction of radiomics features can reveal many of the clinical information hidden in layers of images that were difficult to identify [10, 11]. Research on radiomics can provide tumor characteristics, heterogeneous charac-

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teristics of each treatment method, patient prognosis, and assessment of factors affecting survival [10]. As such, research using medical images as biomarkers have been developed into a new field of study based on the correlation of image parameters and patient information [12]. In this study, we introduce general radiomics methods, clinical cases applicable, and the future of radiomics.

2. Material and Methods

In general, radiomics are non-invasive methods for performing surgical planning, patient survival analysis, and survival prediction extracting from medical images by using specific programs or algorithms to extract quantitative features (called texture features) in the tumor and analyze them together with the patient's clinical or genetic information to diagnose, detect potential phenotypes, and select surgical methods.

Radiomics data can be used to make predictions of clinical models, and this series of processes requires collaborative efforts by radiologists, computer scientists, oncologists, and statistical analysts. The necessary each steps for radiomics analysis are as follows.

2.1. Procedure of Radiomics

2.1.1. Image acquisition

The first step of radiomics is to collect appropriate medical images for the target tumor. The best medical images for the target tumors should be selected and a wide range of parameters (spatial resolution of images, administration and concentration of contrast media, slice thickness, size of matrix or voxel etc. for CT, sequence type, echo time, repetition time, type of image, number of excitation or relaxation, and other sequence of parameters for MRI, type of used nuclide, nuclide activity, standard uptake value, during time after injection, etc. for PET) applied to the acquisition of the image. Each type of images has a different reconstruction algorithm and parameters. Thus users are defined that can adjust them appropriately because there may be several variations in each institution or in individual patients [13]. As a result, if images acquired using different acquisition protocols, even in the same institution, or with different scanners in different patient populations, even with the same disease, affect accurate results by reflecting different biological tissue characteristics of the image functions. Therefore, since it is possible to display different values when extracting radiomics features by performing repeated measurements under the same conditions, it may be better to exclude factors affected by the image collection process and reconstruction parameters from the beginning.

2.1.2. Segmentation

Segmentation is an important step of the radiomics because feature datas are extracted from the segmented volumes. Since many tumors have unclear borders, reviewing them after automatic segmentation process is essential and need to sophisticated segmentation in case of manual process [14]. The initial step for segmentation is to select a Region of Interest (ROI), including the entire tumor or sub-regions affected by tumor metastasis. In general, the selection of the region of interest is not a problem without a difficulty in solid tumors, but in the case of adenocarcinoma or squamous cell carcinoma, it is difficult to establish the ROI because the boundary is not clear [15].

There are several things to consider depending on the type of tumor and the site of primary. For example, in the lungs, attention should be paid to the entire lung area and each segmented lobe area. In the case of head and neck cancer, the tumor is small and has spread to many places.

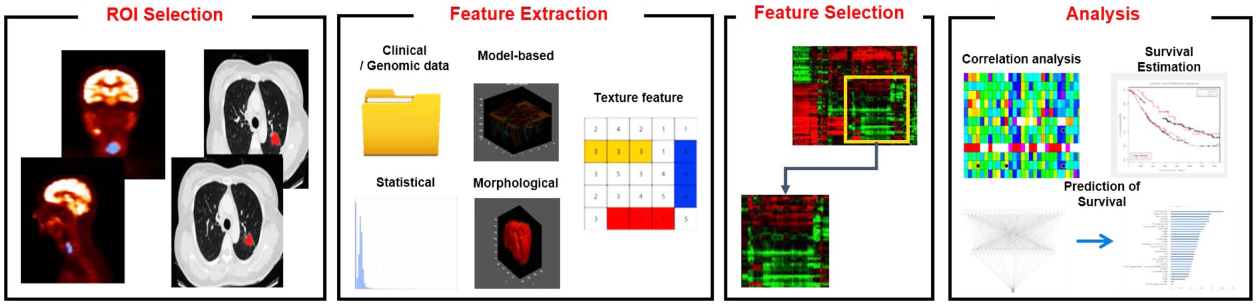
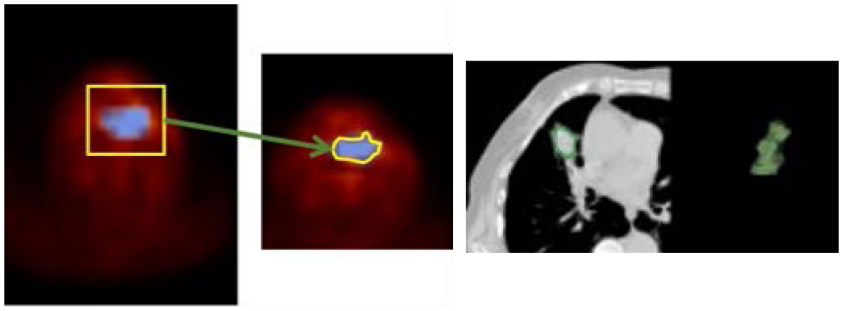


Fig. 1. (Color online) Workflow of radiomics in oncology. After select image types such as PET, CT, PET/CT, and MRI etc. segmentation is performed after ROI selection for tumor segmentation. Radiomics features can be extracted within defined tumor contours on images. Statistical analysis, such as correlation analysis between extracted radiomics features and clinical or genomic data, or morphological analysis, such as morphological analysis and model-based analysis, are performed and select specific features. After that, the clinical images can be analyzed for tumor-influencing factors, survival analysis and prediction etc. depending on the results that can appear between radiomics features.



(A) (B)

Fig. 2. (Color online) An example of manual segmentation of HNSCC (Head and Neck Squamous Cell Carcinoma) of positron emission tomography and automatic segmentation of lung cancer of computed tomography images. Although manual segmentation is true, but (A) image do not show precise borders for tumor regions compared to (B) images.

Therefore, the error caused by setting ROI of normal tissue should be minimized. In addition, segmentation after manual ROI selection takes a lot of time, it is recommended to use program coding or an automation method through an application program. In addition, segmentation after manual ROI selection takes a lot of time, it is recommended to use program coding or an automation method through an application program. Using houns-field Unit threshold (cut-off) pixel or voxel value and spatial resolution for CT images, selecting images according to the necessary lesion such as T1, T2, fmri for MRI images, in case of PET images, using SUV cut-off threshold value is one of the general methods.

2.1.3. Feature Extraction and Selection

After segmentation, various radiomics features can be extracted through the separated region. Quantitative and objective numerical properties clearly demonstrate the use and benefits of radiomics in the field of oncology. Patterns of tumors that are difficult to observe by human can be found through feature values, and are constantly being improved and developed [16]. After extracting a large number of radiomics features, the available features should be selected. The complete implementation of the research using radiomics features is still ongoing, but is known to be related to cancer detection and diagnosis, patient prognosis assessment and appropriate surgical methods [16, 17]. In general, it is possible to select from the correlation with clinical data or genetic data of the patient, and statistical methods such as commonly use methods are least absolute shrinkage and selection operator, principle component analysis, and random forest.

2.1.4. Statistical Analysis

The ultimate goal of radiomics is to determine the patient's clinical analysis (operate method, dosage, frequency of operation, etc.) and survival (alive period and survival prediction) through objective and quantitative values. It is important to understand the correlation between clinical data (living environment, menstruation, tumor progression, location of primary tumor, etc.) and radimoics features extracted from medical images and genetic information data, and to derive appropriate research results.

Spearman's correlation analysis, Pearson correlation analysis, etc. are statistical analysis for identifying correlations between data. When two or more images are mixed, intra-class correlation coefficient (ICC) is used. Kaplan-Meier survival analysis can be used to track patient survival, and then regression analysis can be performed. In addition, multivariate analysis may be used to make predictions of patient survival using feature and clinical or genetic data. Since the result obtained through statistical analysis is expressed through a numerous of numbers, it is mainly represented by a graph such as a heat-map for comparison and analysis of the prediction result.

3. Types of Radiomics Feature

The radimoics features that can be derived from medical images are infinite. The type of features can be classified into four categories according to the meaning of each values in images: (1) morphological, (2) statistical, (3) regional, and (4) skeleton features [18].

3.1. Morphological

Morphological features provide physical information such as tumor shape and volume, and can be divided into higher-order statistical (texture) features based on first-order statistical (histogram) features. For example, features such as spherical imbalance, globular and discrete small size of tumors can be quantified through morphological

features [1]. The surface region of tumors can be measured by triangulation, which completely covers the surface of the tumor, and Gaussian-Laplacian spatial filtering improves the positional characteristics around the tumor and provide fine marginal characteristics between the surrounding normal and tumor tissues [19].

3.2. Statistical

Based on the histogram, the pixels or voxels in the tumors ROI regions that appear along the reference axis have their respective attenuation values along the other axis.

It can be divided into first-order statistical features representing a simple plot of the frequency of pixels and higher-order texture features representing individual spatial image information for each voxels. First-order statistical features (mean, median, contrast, energy, entropy, uniformity, etc.) are most widely used in traditional radiomics and have the advantage of quantifying subtle changes in tumor tissue for each voxels but it can lead to loss of spatial information. GLCM(Gray level Co-occurrence Matrix) of higher-order texture features consists of number, distance, and angle of gray level combinations in images, and is considered of the arrangements pairs of voxels to calculate textures. It can extract features such as energy, entropy, and contrast.

$$GLCM_{\Delta x,\Delta y}(i,j) = \frac{1}{Paris_{ROI}} \sum_{p=1}^{N-\Delta x} \sum_{q=1}^{M-\Delta y}$$

$$\begin{cases} 1 = \text{if } I(p,q) = i,\ I(p+\Delta x, q+\Delta y) = j \\ \quad \text{and } I(p,q),\ I(p+\Delta x, q+\Delta y) \in ROI \\ 0 = otherwise \end{cases}$$

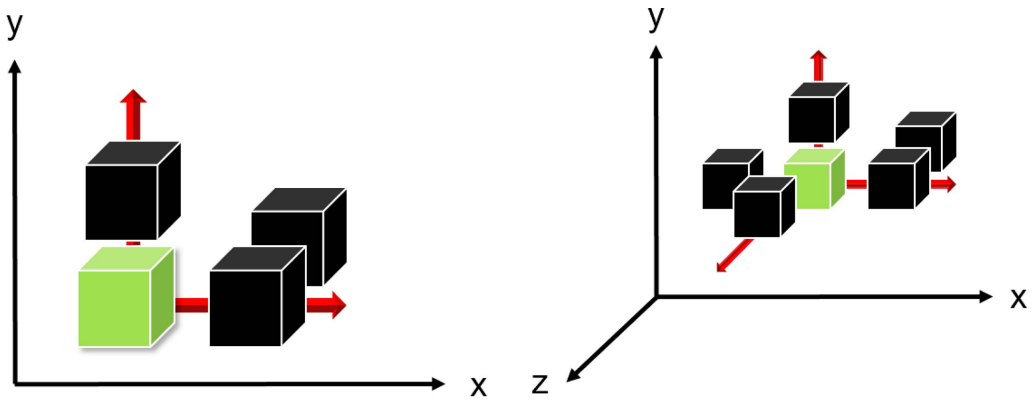
where $I(p, q)$ corresponds to voxel(p, q) in an image(I) of size $N*M$. The vector $\vec{d} = (\Delta x, \Delta y)$ covers the 4 directions in 2D or 13 directions in 3D space. The corresponds to the number of all voxel pairs in region of interest (ROI) [18]. GLRLM (The Grey-Level run Length Matrix) shows continuous voxel specificity of gray levels at all angles, and features such as long-term emphasis, short-term emphasis, non-uniformity of gray levels, and percentage of execution could be extracted [20]. NGTDM represents the degree of similarity of voxel strength of adjacent parts based on one voxel and includes congestion, complexity, and texture strength characteristics. There are also a number of higher-order texture features, each with their own characteristics.

3.3. Regional

Regional features represent quantification between adjacent pixels or voxel in an image and are mainly extracted using a mathematical modeling approach. There might be a variety of heterogeneities within a single or same type of tumors, which is important for radiomics outcomes. Therefore, it should be possible to accurately characterize the spatial distribution of similar gray intensity in the tumor [21].

3.4. Skeleton

It provides information about the tumor shape in organs and tissues, thickness, and deformation where the tumor develops. It can be used in computer morphology analysis, and precisely locates and calculates tumors through quantitative measurement and segmentation of relevant organs and tissues [22].



(A) 2D voxel direction (B) 3D voxel direction

Fig. 3. (Color online) 2D, 3D voxel (green) and associated direction along each axis (x, y, z). Statistical texture features (ex. glcm, glrlm, and ngtdm) are defined according to the relationship between the constant directionality and the surrounding voxels, and the matrix or pixel in the image may be summarized as such concepts.

4. Application of Clinical Case of Radiomics in Oncology

Research through radiomics can be applied to various clinical tumor cases. Here are some clinical cases that can be actively applied.

4.1. Lung-GGO

In generally, early lung carcinomas and precursors are in the form of GGO or have partially solid nodules. In other words, medical images of GGO shows that it can reflect the progression from invasive lesions induced by accumulation of gene mutations. According to many previous studies, visual and objective assessment in pixel or voxel using quantitative radiomics analysis may be helpful in finding small pathologically invasive components that are difficult to evaluate [23]. The mainly used image types are CT images and the same entropy or high attenuation value as the CT attenuation value shown in the histogram has been reported as a major distinguishing factor of lung adenocarcinoma. In addition, a recent study, the ROI setting of 18F-FDG PET/CT was performed to separate high-risk upper and lower regions diagnosed in lung cancer and in related to genetic modification such as tumor size and transformation radiomics analysis are applied as a main method for predicting meta-gene [24]. Non-invasive analysis and research through radiomics in lung cancer and the prediction of lung tumor growth are no longer difficult.

4.2. Head and Neck–HNSCC

HNSCC (Head and neck squamous cell carcinoma) can occur in the head and neck, including the pharynx and larynx, except for the eye ball, brain, ear, and esophagus etc.

Cancer can develop covering the head and neck mucosa, including frontal sinus, nasal, oral cavity, tongue, salivary glands, and adjacent areas. It is known for more than thirty places [25]. Survival and tumor progression of patients can be grasped through radiomics using clinical data such as smoking, drinking, HPV, age, site of primary etc. and images from CT, MRI (T1, T2) and PET/CT [26-28]. In general, head and neck cancers, including squamous cell carcinoma (SCC), such as HNSCC, have a rapid progression of tumor metastasis, and the predictive value of patho-physiological analysis may be low and the result may not be accurately reflected. Mostly CT and MRI images are used, but recently, 18F-FDG PET/CT or sing PET is used to identify the high-risk upper/lower regions according to the risk of tumor by setting ROI of high tumor uptake rate is going on.

4.3. Liver

Research on liver tumors focuses primarily on tissue analysis, and quantitative analysis through images is limited. Most studies have focused on the relation between radiomics features from medical image and clinical characteristics, including survival, recurrence, and treatment response after chemotherapy, but rarely deal with the relation between genomic data and radiomics features from medical images [29]. The study is focused on HCC, which is the most common disease among liver tumors, and use partial results of radiomics features from MRI images and total CT images texture features, or threshold values calculated through ICC statistical analysis by analyzing two types of images, respectively [30]. HCC have a risk leading to end-stage liver disease with minimal symptoms early and is known to have heterogeneity within or between individuals (TP53, TOP2A, CTNNB1, CDKN2A AND AKT1 ETC) [28].

Therefore, predicting the biological progression of HCC through correlation analysis between genetic data and radiomics feature can be effective for proper treatment and prevention. Further research is expected to correlate

Table 1. Literature lists recently in study through radiomics and radiogenomics.

Author	Type of Radiomics	Country	Cancer type	Number of patients	Image modality
Xue *et al.* (2019)	Radiomics	China	Nasopharynx	303	MR
Chao *et al.* (2019)	Radiomics	China	HNSCC	113	CT
Wei *et al.* (2018)	Radiomics	China	Lung-GGO	109	CT
Xia *et al.* (2018)	Radio-genomics	China	HCC	40	CT
Chan *et al.* (2017)	Radiomics	Taiwan	Nasopharynx	101	PET
Dong *et al.* (2017)	Radiomics	China	SqCC	116	PET
Lemarignier *et al.* (2017)	Radiomics	France	Breast Cancer	170	PET
Hui *et al.* (2017)	Radiomics	Singapore	HCC	57	MR
Kim *et al.* (2016)	Radiomics	Korea	Parotid gland	46	PET
Ha *et al.* (2014)	Radiomics	Korea	ADC	30	PET

with clinical data such as patient prognosis, tumor size and growth, and clinical data such as microvascular invasion and pathological grade.

5. Conclusion and Future Aspects

Radiomics have developed through various methods and can apply various clinical cases, but some tumors may still be in their infancy. In the early stages of radiomics analysis, the characteristics were found to be mostly unstable and texture features were not classified. However, there are many efforts have been made to continuously improve standardization and classify according to texture feature features [31-33]. At present, most studies through radiomics are carried out by extracting features from a single modality of medical image, but there is the possibility to apply texture features extracted from several different type of medical image simultaneously using a variety of analytical methods. By combining genetic datas (anatomical, functional and metabolic, etc.), clinical data (age, living environment, location of primary tumor, tumor progression, surgical status, etc.) and radiomics features from medical images, the results of research of radiomics fields can provide diagnose and classify of tumors useful information on oncology in connection with predicting treatment response, predicting patient survival. Above all, the processes can be provided non-invasively, and the results of analysis can be produced by quantitative and objective indicators, not by the subjective opinion of inspectors and the reader. For more accurate study, Collaboration with experts in various fields such as statisticians, computer programmers and medical scientists is an essential.

In conclusion, the role of radiomics is growing in oncology using texture features extracted from medical images more than ever, and radiomics data offers the potential in a wider variety of ways. Therefore, radiomics will be regarded to occupy an essential position in the development of precision medicine in the oncology field in the near future [34].

References

[1] G. W. Lee, S. H. Bak, and H. Y. Lee, Nucl. Med. Mol. Imaging. **52**, 2 (2018).
[2] C. Christina, S. P. Shah, S. F. Chin, G. Turashvili, O. M. Rueda, M. J. Dunning, D. Speed, A. G. Lynch, S. Samarajiwa, Y. Yuan, S. Gräf, G. Ha, G. Haffari, A. Bashashati, R. Russell, S. McKinney, METABRIC Group, A. Langerød, A. Green, E. Provenzano, G. Wishart, S. Pinder, P. Watson, F. Markowetz, L. Murphy, I. Ellis, A. Purushotham, A. L. Børresen-Dale, J. D. Brenton, S. Tavaré, C. Caldas, and S. Aparicio, Nature **486**, 7403 (2012).
[3] Cancer Genome Atlas Research Network, Nature **511**, 7511 (2014).
[4] Cancer Genome Atlas Research Network, Nature **489**, 7417 (2012).
[5] H. Hedvig, Radiology **259**, 3 (2011).
[6] B. Sharma, A. Martin, S. Stanway, S. R. Johnston, and A. Constantinidou, Nat. Rev. Clin. Oncol. **9**, 12 (2012).
[7] T. Tirkes, M. A. Hollar, M. Tann, M. D. Kohli, F. Akisik, and K. Sandrasegaran, Radiographics **33**, 5 (2013).
[8] N. McGranahan and C. Swanton, Cell **168**, 4 (2017).
[9] J. P. O'Connor, C. J. Rose, J. C. Waterton, R. A. Carano, G. J. Parker, and A. Jackson, Clin. Cancer. Res. **21**, 2 (2015).
[10] Y. S. Chong, J. H. Kim, H. Y. Lee, Y. C. Ahn, K. S. Lee, M. J. Ahn, J. Kim, Y. M. Shim, J. Han, and Y. L. Choi, PLoS ONE. **9**, 2 (2014).
[11] J. Y. Son, H. Y. Lee, J. H. Kim, J. Han, J. Y. Jeong, and O. J. Kwon, Eur. Radiol. **26**, 1 (2016).
[12] H. X. Bai, A. M. Lee, L. Yang, P. Zhang, C. Davatzikos, J. M. Maris, and S. J. Diskin, Br. J. Radiol. **89**, 1061 (2016).
[13] S. Rizzo, F. Botta, S. Raimondi, D. Origgi, C. Fanciullo, A. G. Morganti, and M. Bellomi, Eur. Radiol. Exp. **2**, 36 (2018).
[14] R. J. Gillies, P. E. Kinahan, and H. Hricak, Radiology **278**, 2 (2016).
[15] E. Rios Velazquez, H. J. Aerts, Y. Gu, D. B. Goldgof, D. De Ruysscher, A. Dekker, R. Korn, R. J. Gillies, and P. Lambin, Radiother Oncol. **105**, 2 (2012).
[16] G. W. Lee, H. Y. Lee, H. J. Park, M. L. Schiebler, E. J. R. van Beek, Y. Ohno, J. B. Seo, and A. Leung, Eur. J. Radiol. **86**, 297 (2017).
[17] H. J. Hugo, R. V. Emmanuel, R. Velazquez, R. T. H. Leijenaar, C. Parmar, P. Grossmann, S. Carvalho, J. Bussink, R. Monshouwer, B. Haibe-Kains, D. Rietveld, F. Hoebers, M. M. Rietbergen, C. R. Leemans, A. Dekker, J. Quackenbush, R. J. Gillies, and P. Lambin, Nature Communications **5**, 4006 (2014).
[18] B. de Hoop, H. Gietema, S. van de Vorst, K. Murphy, R. J. van Klaveren, and M. Prokop, Radiology **255**, 1 (2010).
[19] J. Park, Y. Kobayashi, K. Y. Urayama, H. Yamaura, Y. Yatabe, and T. Hida, PLoS One. **12**, 11 (2016).
[20] C. Nioche, F. Orlhac, and I. Buvat, Texture-User Guide Local Image Features Extraction, LIFEx, France (2019).
[21] M. R. Divine, P. Katiyar, U. Kohlhofer, L. Quintanilla-Martinez, J. A. Disselhorst, and B. J. Pichler, J. Nucl. Med. **57**, 3 (2015).
[22] S. Gu, Z. Wang, J. M. Siegfried, D. Wilson, W. L. Bigbee, and J. Pu, Int. J. Biomed. Imaging. (2012).
[23] J. P. Ko, J. Suh, O. Ibidapo, J. G. Escalon, J. Y. Li, H. Pass, Naidich. David P, Bernard Crawford, B. Tsail. Emily, W.K. Chi, Artem Mikheev, and Henry Rusinek, Radiology **280**, 3 (2016).
[24] J. Wu, M. F. Michael, X. Dong, D. L. Rubin, S. Napel,

M. Diehn, B. W. Jr Loo, and R. Li, Int. J. Radiat. Oncol. Biol. Phys. **95**, 5 (2016).
[25] Y. S. Lee, Korean J. Otorhinolaryngol-Head Neck Surg. **62**, 9 (2019).
[26] X. Qian, B. Sinikovic, F. Schreiber, S. Ochsenreither, K. Klinghammer, B. Wollenberg, A. M. Kaufmann, and A. E. Albers, Eur. Arch. Otorhinolaryngol. **275**, 11 (2018).
[27] N. Subramaniam, S. Murthy, D. Balasubramanian, T. H. Low, S. Vidhyadharan, J. R. Clark, K. Thankaapan, and S. Lyer, Head Neck. **40**, 10 (2018).
[28] Q. S. Xu, C. Wang, B. Li, J. Z. Li, M. H. Mao, L. Z. Qin, H. Li, X. Huang, Z. Han, and Z. Feng, Oral Dis. **24**, 3 (2018).
[29] C. S. An, G. Rakhmonova, J. Y. Choi, and M. J. Kim, Clin. Mol. Hepatol. **22**, 2 (2016).
[30] K. M. Elsayes, J. C. Hooker, M. M. Agrons, A. Z. Kielar, A. Tang, and K. J. Fowler, Radiographics **37**, 7 (2017).
[31] F. Tixier, M. Hatt, C. Le Rest, A. Le Pogam, L. Corcos, and D. Visvikis, J. Nucl. Med. **53**, 5 (2012).
[32] Y. Balagurunathan, Y. Gu, H. Wang, V. Kumar, O. Grove, S. Hawkins, J. Kim, D. B. Goldgof, L. O. Hall, R. A. Gatenby, and R. J. Gillies, Transl. Oncol. **7**, 1 (2014).
[33] Y. Balagurunathan, V. Kumar, Y. H. Gu, J. Kim, H. Wang, Y. Liu, D. B. Goldg, L. O. Hall, R. Korn, B. Zhao, L. H. Schwartz, S. Basu, S. Eschrich, R. A. Gatenby, R. J. Gillies, J. Digit. Imaging **27**, 6 (2014).
[34] H. Arimura, M. Soufi, H. Kamezawa, K. Ninomiya, and M. Yamada, J. Radiat. Res. **60**, 1 (2019).