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Feeding the data monster: data science in head and neck cancer for personalized therapy.

Abstract

Objective: Head and neck carcinomas are clinically challenging malignancies due to tumour heterogeneities and resilient tumour subvolumes that require individualized treatment planning and delivery for an improved outcome. While current approaches to diagnosis and therapy have boosted locoregional control, the long-term survival in this patient group remains unchanged over the last decades. A new approach to head and neck cancer management is therefore needed to better identify patient subgroups that are responsive to specific therapies. The aim of this paper is to review the current status of knowledge and practice utilizing big data towards personalized therapy in head and neck cancers based on CT and PET imaging modalities.

Methods: Search of literature published in English since 2000 was conducted using Medline. Additional articles were retrieved via pearling of identified literature. Manuscripts were reviewed and summarized in tabulated format.

Results: Studies based on big data in head and neck cancer are limited, however, the field of radiomics is under continuous development and provides valuable input for personalized treatment. Using PET/PET CT biomarkers for patient treatment individualization and response prediction appears promising, especially in regards to detection of hypoxia and clonogenic cancer stem cells. Literature shows that macroscopic changes in medical images (whether structural or functional) are correlated with biological and biochemical changes within a tumour

Discussion and Conclusions: Current trends in data science suggest that the ideal model for decision support in HNC should be based on human-machine collaboration, namely on: (1) software-based algorithms, (2) physician innovation collaboratives, and (3) clinician mix optimization.

Key words: radiomics; head and neck cancer; human papilloma virus; patient stratification; outcome prediction

1. Big data based on imaging techniques in head and neck cancer

Several publications investigated the use of data mining and machine learning on specific cancers. This paper aims to review the current status of knowledge and practice utilizing big data towards personalized therapy in head and neck cancers. While the applications and limitations of MRI radiomics in head and neck cancer have been recently explored[1], the main focus of the current work is on the potential of CT and PET radiomics to revolutionize the management of HNC.

Head and neck cancers (HNC) continue to be the most clinically challenging malignancies. This is owing to several factors, including: (1) late detection, (2) heterogeneous tumour subtypes which respond distinctively to treatment, (3) difficult anatomical locations leading to adverse events, (4) risk factors resulting in tumour recurrence, and (5) comorbidities. While tumour targeting technologies are slowly reaching their developmental peak, the question that still remains is what are we really targeting? What exactly is inside the tumour that dictates varied treatment responses from individuals having the same tumour classification? How much is the tumour's texture, shape and phenotype influencing treatment outcome? The answers to these questions can only be given by the analysis of the complex interplay between those parameters that act on a micro-level and those that arbitrate from a macro-level. There is, therefore, need for complex omics analysis of all parameters that influence specific tumour growth, progression and behaviour during treatment (microscale), together with the assessment of epigenetic, patient-specific factors that additionally contribute to the overall response to therapy (macroscale). The few available biomarkers related to tumour response in HNC, such as tumour hypoxia, the human papilloma virus (HPV) infection, the overexpression of epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF), are all valuable contributors to outcome prediction[2,3]. Nevertheless, the pronounced intratumour heterogeneity, seldomly reflected by the above biomarkers, requires novel investigational approaches.

Personalized treatment planning and delivery is not a new concept in HNC. Yet, a comprehensive personalized therapy must be built on results derived from big data analysis, which is still a work in progress in head and neck oncology. A recent study encompassing the results of a questionnaire sent to major international collaborative research groups on HNC totaling about 100 key players showed that big data are not commonly used in HNC research[4]. The main sources for big data harvesting include genomics, radiomics, clinical studies and epidemiology (table 1), with the most researched area being the medical imaging-based radiomics.

2. Methods

A search strategy for Medline was developed to identify articles using big data mining and radiomics for patients with HNC. The final search strategy included the following limitations: limited to humans, English, published from 2000 onwards. Reference pearling was conducted using the identified articles. Duplications and conference abstracts only were removed. Paper selection was then conducted via referring to the title and abstract, and involved the exclusion of non-head and neck cancers, and theoretical studies. The identified articles (25) were retrieved, analyzed and summarized in a tabulated manner. Because of the small number of articles and large variations in study designs, statistical analysis of data has not been possible. Consequently, this manuscript is an integrative/scoping review that summarizes and evaluates the accumulated current status of knowledge in big data/radiomics for head and neck cancers.

3. Data mining in CT

One of the first comprehensive studies that assessed the relevance of various radiomics features in HNC was reported by Aerts *et al* showing that radiomics-born data offer powerful prognostic information associated with tumour-specific gene expression patterns[5]. Based on these observations, Parmar *et al* assessed the potential of radiomics in predicting overall survival after HNC on two independent cohorts (one training and one validation cohort) of a combined 196 patients using feature selection and classification training centered on 440 radiomic features from the segmented tumour regions: texture, first order intensity statistics and shape of tumour region on CT images[6]. To evaluate the prognostic performance of different feature selection and classification methods, the area under receiver operating characteristics curves (AUC) was used, whereas stability against data perturbation was assessed using hard data perturbation setting (for feature selection stability) and the relative standard deviation and bootstrap approach (for classifier stability assessment). The study highlighted the importance of radiomics-based machine learning models for clinical decision support and the potential of identifying the optimal machine learning techniques for HNC by comparing various methods using independent radiomic cohorts[6,7].

Knowing that ***tumour hypoxia*** is one of the most common features investigated in relation to head and neck malignancies, it is not surprising that this parameter is also explored for its radiomic signature and possible predictive value. In a preclinical radiogenomics study involving an *in vivo* hypoxic tumour model, Panth *et al* [8] hypothesized that there is not only a correlation but a causality between patient-specific genetic factors and image features before and after radiotherapy. The study was based on the observation whereby hypoxic conditions change upon the administration of doxycycline (an indirect inhibitor of the eIF2α signaling pathway required for hypoxic cell survival), resulting in a diminished tolerance for hypoxia, thus decreased hypoxic fraction. It was observed that doxycycline induces genetic changes that result in different radiomics features in the drug-treated versus the non-treated tumours. Further CT image features varied between the combined RT-doxycycline and the RT-monotherapy tumours. The difference in post irradiation tumour heterogeneity between drug-induced (genetic change) and non-induced tumours translated into different imaging features suggested to be due to phenotypic changes[8]. Accordingly, radiomics enables quantification of genetic changes in tumours during early treatment, which can assist in outcome prediction and potential treatment adjustment.

Contrast enhanced CT radiomics features combined with ^{18}F-FDG have been investigated for their potential use as surrogates for ^{18}F-FMISO, a tumour hypoxia specific PET radiotracer that is not as widely available as the gold standard FDG[9]. While universally used in PET imaging for HNC staging and differentiation, FDG is not a tracer for hypoxia[10], therefore additional CT-based features are needed for the quantification of tumour oxygenation status. Images from 75 HNC patients encompassing 121 lesions were employed for machine learning (79 lesions for training a LASSO regression model and 42 for testing). The most predictive FDG-PET features identified were the 90th percentile and the skewness of the SUV distribution, while from CT images: the long-run, high-gray-level emphasis of the volume of interest for which SUV > 42% SUV_{max} and the volume taken by voxels with HU > 70 within the low-SUV volume (SUV < 42% SUV_{max}). The tested models were evaluated by AUC, with the highest value of 0.873 resulting from a

radiomics signature that combines features from the two imaging techniques (the 90th percentile of the SUV distribution (from PET) and the long-run, high-gray-level emphasis of the high-dose region (from CT)). Consequently, the study showed that the addition of contrast enhanced CT features to those from FDG-PET provides information on hypoxia status comparable to ^{18}F-FMISO T/B (tumour-to-blood uptake ratio), thus offering a potential biomarker for those clinics where hypoxia-specific tracers are not available.

Different anatomical sites among HNC patients present with different risk factors, radiobiological features and clinical challenges. The relatively new variable among the already large arsenal of parameters, the ***human papilloma virus***, further complicated the treatment scenario and required adjustments of conventional staging systems for HNC[11]. Given that HPV positive HNC (particularly oropharyngeal cancers, predominantly HPV/p16) respond better to both radiation and chemotherapy[12,13] several studies investigated the potential of radiomics to quantitatively assess the differences in image patterns between HPV+ and HPV- HNC patients. One of the first studies undertaken consisted of a blinded matched-pair analysis evaluating 136 pretreatment CT images for pattern disparities among patients with different HPV status. The study revealed that HPV+ tumours present with well-defined borders, whereas HPV- have poorly-defined borders with increased tendency towards invasion into adjacent muscle tissue[14]. While this study investigated HPV-related radiological differences on a larger scale, other groups considered a more detailed image texture analysis to reveal new information.

Based on contrast-enhanced CT images originating from 40 patients with primary oropharyngeal squamous cell carcinoma and known HPV status (29 HPV+ patients), Buch *et al* observed significant differences in texture features as a function of HPV[15]. The conclusion was based on texture analysis (e.g. subtle CT attenuation among image pixels) of 42 features from each segmented volume of the primary tumour. Statistically significant differences were found in the histogram feature median ($p = .006$), histogram feature entropy ($p = .016$) and gray-level co-occurrence matrix features ($p = .043$)[15]. Further radiomic investigations on 46 non-oropharyngeal cancer patients with known HPV status that underwent contrast-enhanced CT for initial staging, allowed the identification of texture parameters that differentiate between HPV+ and HPV- tumours in these patients[16]. Significant differences were shown by 16 out of 42 texture parameters: 5 histogram features ($p \leq .03$), 3 gray-level co-occurrence matrix features ($p \leq .02$), one gray-level run-length feature ($p = .009$), 2 gray-level gradient matrix features ($p \leq .02$) and 5 Law features ($p \leq .04$). These results have demonstrated that HPV status-based morphologic differences exists even in non-oropharyngeal cancers.

Lately, new interest is shown towards the radiomics features of ***primary tumour volume*** and its correlation to site-specific locoregional control. A recently published study by the MD Anderson Cancer Centre Head and Neck Quantitative Imaging Working Group[17] reported on the radiomic signatures for local recurrence extracted from CT scans of 465 oropharyngeal cancer patients. By performing texture analysis on pretreatment contrast CT images using a Matlab platform-based imaging biomarker explorer software, the group identified two image features to serve as independent predictive factors of locoregional control: (1) the co-occurrence matrix (derived from gray-level image histogram analysis) and (2) the absolute gradient (spatial variation of grey-level values)[17]. While not limitation-free, this work is a valuable step towards risk stratification refinement and personalized treatment in HNC patients based on radiomics features. Previously,

Zhang *et al* investigated the potential of CT texture and histogram measurements of the primary tumour to show association with overall survival in 72 locally advanced HNC patients treated with induction chemotherapy[18]. Of the investigated CT texture features, primary mass entropy and skewness were found to be independent predictors of overall survival.

Beside predicting tumour control, radiomic features could potentially serve as tools in the projection of adverse events. Structural modifications induced by HNC radiotherapy among organs at risk can have significant impact on patient's quality of life. To evaluate such changes in the parotid glands of 21 patients treated with radiotherapy for nasopharyngeal cancer, CT-based textural parameters were analysed, suggesting that early variations of CT features such as mean intensity and fractal dimension, could predict shrinkage of the parotid during radiotherapy[19]. Using discriminant analysis based on volume and fractal dimension, the model predicted the final parotid shrinkage with a 71.4% accuracy. These findings can assist in the identification of patients that are at increased risk of xerostomia.

4. Data mining in PET

To attain a more comprehensive clinical scenario, the structural/anatomical information originating from CT texture analysis should be considered together with the functional data revealed by PET image breakdown. Owing to the valuable and complex information offered, PET/CT became a critical tool for HNC staging, stratification, treatment planning and monitoring.

One of the earliest works in PET/CT radiomics related to HNC aimed to improve the accuracy of treatment planning through reduction of target delineation uncertainties and interobserver variability using automated segmentation with image texture analysis[20]. A segmentation system using co-registered multimodality pattern analysis (COMPASS) was developed to automatically delineate tumour targets in HNC on PET and CT images and to be compared with clinically available threshold-based methods and radiologist-drawn contours. A number of 27 features (first-, second-, high-order and structural) were extracted from PET and CT images, concluding that coarseness, contrast and busyness had the highest distinguishing power between normal and tumour tissue. The best tissue classification was offered by the combined PET/CT features.

A number of studies were undertaken using radiomic features to investigate various attributes of PET/CT images, such as: tumour classification, outcome prediction, risk analysis, as well as the advantage of combined PET/CT over single modality imaging techniques (table 2).

The value of pretreatment functional imaging radiomics (from PET) as compared to structural imaging features (from CT) for the modelling of local tumour control was assessed in a cohort of 172 HNC patients (121 patients for the training cohort and 51 patients in the validation cohort) treated with chemoradiotherapy[21]. All patients underwent both ^{18}F-FDG-PET imaging and contrast enhanced CT, images that were segmented and analysed by an in-house developed radiomics software that allowed four types of feature extraction: shape, intensity, texture and wavelet transform, totaling 569 CT and 569 PET radiomic features for each patient. For comparative purpose, three models were trained for prediction of local tumour control: CT-based, PET-based and a combined PET/CT model. The most predictive features for the CT model were heterogeneity in CT density (suggested to be linked to cell proliferation and hypoxia) and HLH intensity, while

for the PET model – spherical disproportion and gray-level size-zone texture matrices (correlated with FGD uptake). While both CT and PET models presented equally good discriminative power of the local tumour control, and stratification into risk groups, the CT model overestimated the probability of tumour control in the high-risk group due to CT artifacts in the tumour region. Interestingly enough, the study concluded that the combination of CT with FDG-PET radiomics features brought no additional benefit as compared to either of the imaging techniques alone[21].

Similarly, Vallières *et al* developed radiomics-based predictive models to evaluate the risk of locoregional recurrences and distant metastases prior to chemoradiotherapy in HNC patients[22]. A number of 1615 radiomic features were extracted from the gross tumour volume of PET/CT images originating from 300 patients. Their results showed that no radiomic features were significantly associated with locoregional recurrence, whereas 63% (from PET) and 61% (from CT) features correlated with the risk of distant metastases. However clinical variables such as staging, age and HPV infection were all significantly associated with both locoregional recurrence and metastases, showing the importance of combining image-derived features with clinical variables for a complete picture regarding the outcome.

Textural features of pre-treatment FDG-PET/CT images were analysed for their prognostic value in 70 advanced stage oropharyngeal cancer patients[23]. The study aimed to find any radiomic features that could add predictive value to the total lesion glycolysis (TLG), considered a prognostic indicator in this patient group. The analysed textural features were extracted from histograms, gray-level co-occurrence matrix and neighborhood gray-tone difference matrix, while AUCs were employed to identify the cutoff values for these features and TLG. Of all evaluated parameters, uniformity (derived from normalized gray-level co-occurrence matrix) and TLG were independently correlated with treatment outcome. Accordingly, this study has led to a prognostic system, showing that patients with TLG > 121.9 g and uniformity ≤ 0.138 have the worst prognosis[23].

Another study evaluated the risk of all-cause mortality, local failure and distant metastasis in a group of 174 oropharyngeal cancer patients following definitive chemoradiotherapy[24]. Overall, 24 features, found representative for the FDG-avid regions, were extracted, including SUV_{max}, quantification of SUV intensity-volume histograms, shape and textural features (gray-level co-occurrence matrix). The model developed for local failure prediction demonstrated robustness through validation on an independent dataset at another institution, despite differences in the patient cohort. The value of this result stays in its potential for patient stratification and treatment adaptation as a function of risk groups.

One of the most explored attributes of PET/CT is ***tumour classification*** and staging. To further promote this quality, Wu et al designed a computerized system for automatic detection on PET/CT of nasopharyngeal carcinomas which targets both the primary tumour and nodal spread[25]. Their system based on 25 sets of images combined radiomics features (average intensity of CT values, FDG intensity) with clinical information (symmetry measures to the medial plane, anatomical location) for tumour classification between physiological and pathological uptakes. True positive results were considered those instances when the algorithm-based lesion volume and the radiologist-delineated volume overlapped at least 80%, which occurred in all but five wrongly classified anatomical regions due to naturally high uptakes by symmetrical organs (such as tonsils).

As mentioned above, a parameter of continuous clinical interest in HNC diagnosis and treatment is ***HPV***, and PET imaging is no exception in this regard. A common biomarker used in PET imaging to quantitatively measure tumour metabolism through FDG uptake is the maximum standard uptake value (SUV_{max}). Since high levels of SUV_{max} in HNC were suggested to correlate with poor outcome[26], in trying to correlate tumour HPV/p16 status to SUV_{max} studies were undertaken to evaluate SUV levels as a function of HPV[27]. PET/CT and HPV/p16 data obtained from 65 patients with oropharyngeal cancer showed that while tumour SUV_{max} between HPV+ and HPV- had no statistically significant variation ($p = 0.28$), the mean nodal SUV_{max} for HPV+ patients was significantly higher than that for the HPV- group (10.8 vs 7.9, $p = 0.02$). This was suggested to be due to the immune response of HPV infected nodes that stimulate high FDG activity. The predictive value of p16 positive disease in patients with nodal $SUV_{max} \geq$ mean SUV_{max} was 92.3%. The study concluded that since the only predictor of HPV status is the nodal SUV_{max}, patients can be stratified for treatment according to the mean SUV_{max} p16+ used as a cutoff value[27]. These results agree with the findings of another study on 22 oropharyngeal and oral cavity cancer patients[28], thus confirming the usefulness of PET data in predicting HPV status. Although, owing to different PET protocols, the cutoff values varied between the two studies, prohibiting therefore the extrapolation of nodal SUV_{max}, these results potentially offer an additional image-based biomarker for patient stratification.

The keys to more robust conclusions are harmonization of PET scanner/image reconstruction, standardization of imaging procedures, and reference normalization to decrease uncertainties of image quantification and increase the power of data reproducibility across clinics[29].

5. Conclusions

Studies based on big data in head and neck cancer are limited, however, the field of radiomics is under continuous development and provides valuable input for personalized treatment. Current research shows that big data is not commonly used in HNC research, however there is a growing interest. The main sources for big data harvesting in HNC include genomics, radiomics, clinical studies and epidemiology, with the most researched area being the medical imaging-based radiomics. While current literature shows that big data and radiomics have potential to better stratify patients with HNC and thus personalize their treatment approaches, more data (more robust and larger datasets) are required prior to broader clinical implementation and/or change in practice.

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Table 1. Big data sources in head and neck oncology

	Source	***Investigative method***	***Aim / application***
Big data sources	Laboratory	Genomics	Identification of risk factors Diagnosis / prognosis Patient stratification Prediction of treatment outcome
	Medical imaging	Radiomics	
	Clinics	Clinical trials	
	Cancer registries	Epidemiology	

Table 2. PET/CT-based radiomics studies in head and neck cancer

Study aim	***Prognostic radiomic features / highest association with endpoint***	***Conclusions***
Image texture analysis for ***treatment planning accuracy improvement*** [20]	PET and CT image coarseness, contrast, busyness	Combined PET/CT radiomic features offered the best tissue classification with high specificity and sensitivity. Tumour delineation using the COMPASS model was best correlated with the radiologist-drawn contours.
Automatic detection of nasopharyngeal carcinomas [25]	Average intensity of CT values; FDG uptake intensity	The system built on combined image-based and clinical features can successfully identify all hypermetabolic lesions, allowing for promising clinical use.
Risk stratification model / **staging** in oropharyngeal carcinomas [23]	Gray-level co-occurrence matrix; Uniformity / coherence	Total lesion glycolysis (TLG), uniformity and HPV infection are significantly associated with overall survival. A risk stratification strategy was developed based on TLG and uniformity.
The role of pre-treatment PET vs CT in ***predicting local control*** [21]	CT density; HLH intensity Spherical disproportion; gray-level size-zone texture matrices	Overestimation of tumour control probability in the high-risk group; no added value from the combined PET/CT as compared to either imaging method alone.
Predictive models to evaluate the ***risk of locoregional recurrences & distant metastases*** [22]	Large zone high gray-level emphasis (CT); Zone size non-uniformity (CT)	No significant correlation between radiomic features and locoregional recurrence. The highest predictive values are given by image-derived features combined with clinical variables.
Predictive models to evaluate the ***risk of all-cause mortality, local failure & distant metastasis*** [24]	Predictive values of image features (statistical, shape, texture) were model-dependent.	The strongest predictive power was given by multiparametric models. The local failure model showed robustness when transposed onto another, independent patient cohort.

Take-Home Points

- Textural features of pre-treatment images of head and neck cancer patients allow the development of tumour-specific biomarkers and gene-expression patterns through radiomics to assist in outcome prediction and personalized treatment.
- Radiomics-based data together with genomics and clinical information will strengthen the multidisciplinary approach towards patient care that is greatly needed in head and neck oncology.
- Ideally, a model for decision support in head and neck cancer should be based on human-machine collaboration, namely on: (1) software-based algorithms, (2) physician innovation collaboratives, and (3) clinician mix optimisation.
- To attain more robust conclusions in the field of radiomics and to improve the quality of data mining, it is imperative to aim towards (1) standardization of imaging procedures and protocols, (2) reference normalization for more accurate image quantification and (3) better data reproducibility. This will decrease uncertainties of image quantification and increase the power of data reproducibility and their significance across clinics.
- These goals will require both qualitatively and quantitatively adequate data, as well as ample training for the interdisciplinary team involved.