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Original article

Prognostic value of combining a quantitative image feature from positron emission tomography with clinical factors in oligometastatic non-small cell lung cancer

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ABSTRACT

Background and purpose: Oligometastatic non-small cell lung cancer (NSCLC) is a heterogeneous condition with few known risk stratification factors. A quantitative imaging feature (QIF) on positron emission tomography (PET), gray-level co-occurrence matrix energy, has been linked with outcome of non-metastatic NSCLC. We hypothesized that GLCM energy would enhance the ability of models comprising standard clinical prognostic factors (CPFs) to stratify oligometastatic patients based on overall survival (OS).

Materials and methods: We assessed 79 patients with oligometastatic NSCLC ($\leq$3 metastases) diagnosed in 2007–2015. The primary and largest metastases at diagnosis were delineated on pretreatment scans with GLCM energy extracted using imaging biomarker explorer (IBEX) software. Iterative stepwise elimination feature selection based on the Akaike information criterion identified the optimal model comprising CPFs for predicting OS in a multivariate Cox proportional hazards model. GLCM energy was tested for improving prediction accuracy.

Results: Energy was a significant predictor of OS ($P = 0.028$) in addition to the selected CPFs. The c-indexes for the CPF-only and CPF + Energy models were 0.720 and 0.739.

Conclusions: Incorporating Energy strengthened a CPF model for predicting OS. These findings support further exploration of QIFs, including markers of the primary tumor vs. those of the metastatic sites.

Outcomes for individual patients with cancer vary even when such patients are matched by cancer type and disease stage [1]. Staging and other population-based risk assessments fail to consider aspects of the increasingly important concept of "personalized medicine." The disease course in a particular individual, and clinical and molecular markers of prognosis, should have a role in medical decision-making, particularly in stage IV oligometastatic disease, as the prognosis for some patients can be substantially better than what that stage typically implies [2].

Non-small cell lung cancer (NSCLC) occasionally manifests with oligometastases, in which metastatic disease appears as a solitary or a few isolated, circumscribed lesions. Conceptually, boundaries on the progression oligometastatic disease are thought to restrict spread to certain organs until those boundaries are overcome [3]. The spread of NSCLC to certain organs is known to have prognostic implications [4,5]. However, differences in prognosis and behavior of various types of oligometastatic NSCLC are just beginning to be recognized [6–8]. Subsequently, treatment recommendations for oligometastatic disease are becoming more distinct from those for typical stage IV disease, with implications that can include aggressive treatment measures such as organ removal [9].

Oligometastatic NSCLC is a heterogeneous disease with substantially differing prognosis, and information that can be used to stratify patients with such disease to receive more aggressive treatment is still limited. Radiographic biomarkers may be one such tool for risk stratification and personalized medical decision-making. Standardized uptake values (SUVs) and metabolic tumor volumes derived from positron emission tomography (PET) have been shown to have prognostic value in NSCLC [10–12]. The utility of SUV has been demonstrated mostly in terms of either absolute values or scan changes from before to after treatment [11,13].

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Recent radiomics studies have demonstrated the effectiveness of quantitative image features for use as biomarkers in radiology. Radiomics has been shown to be predictive of NSCLC pathological response to neoadjuvant chemoradiation, distant metastasis, and mutational status [14–16]. This prognostic value and prediction of response extends to other cancers [17–22], and has led to an interest in usage for radiotherapy individualization [23]. Further, repeatability [24] and prediction of survival has been demonstrated using such features for NSCLC [25,26] with PET-based and CT-based (including cone-beam) features [27,28].

To better facilitate upfront decision-making, one group quantified several metrics indicative of fluorodeoxyglucose (FDG) uptake distribution on PET with the intent of creating prognostic models based solely on pretreatment scans. That group demonstrated that incorporating quantitative imaging features (QIFs) from pretreatment PET scans into models composed of clinical prognostic factors (CPFs) improved the fit and ability of those models to stratify patients with stage III NSCLC in terms of overall survival (OS). Specifically, the primary tumor QIF energy, a feature extracted from the gray-level co-occurrence matrix (GLCM), was found to be selected in all folds of cross-validation [29].

GLCM energy quantifies the uniformity of the SUVs within a primary tumor or metastasis while accounting for the spatial orientation of the voxels [30]. This metric is calculated by determining the probabilities for different voxel-adjacent voxel pairs within the tumor, squaring these values, and summing them together. Therefore, a completely uniform tumor would have an energy value of 1, whereas a heterogeneous tumor in which few adjacent voxels have the same SUV would have an energy value that is very small [30].

We evaluated potential correlations between the GLCM energy and prognosis in a subset of patients with oligometastatic NSCLC. We hypothesized that incorporating GLCM energy as an imaging biomarker into predictive models consisting of CPFs would enhance the ability of those models to stratify patients in terms of OS.

Methods and materials

Patients

Institutional review board approval was granted for this retrospective chart review, and the requirement for informed consent was waived. Patient confidentiality in all cases was maintained in accordance with the Health Insurance Portability and Accountability Act. We originally identified 115 patients with oligometastatic NSCLC ($\leq$3 synchronous or $\leq$3 metachronous metastases) diagnosed at our institution from June 2007 to June 2015. This date range allowed at least 6 months of follow-up time and ensured that all patients' PET scans could undergo three-dimensional reconstruction.

Patients were excluded if PET scans obtained elsewhere were not compatible with the in–house IBEX quantitative imaging software [31]. Patients with metachronous disease required a PET scan of the primary site before treatment was begun. Treatment initiation was defined as the first cycle of chemotherapy for patients receiving induction chemotherapy or the first day of radiation treatment for patients receiving radiation therapy upfront. One patient was excluded because the tumor was inextricable from another benign process, and another 21 patients were excluded for having inadequate PET scans.

Quantitative imaging feature extraction

Owing to the low resolution of PET, quantitative feature extraction from larger lesions yields much more consistent and reproducible results than extraction from smaller lesions. A threshold of $\geq$5 mL has been proposed [29], but restricting our analysis to tumors of this size would have rendered our sample size insufficient. Thus, neither the primary tumor nor the largest metastases, as calculated after IBEX contouring, could be smaller than 2 mL. Exceptions to this threshold were made such that a small metastasis (<2 mL) could be included if a large lymph node was available nearby to use as a proxy (n = 7). Radiomics data have previously demonstrated equivalent or greater prognostic value using lymph nodes as opposed to the primary tumor [32–34]. The exclusion of smaller sites, along with heterogeneity in number of metastases and lymph nodes prevented use of an overall energy in individual patients. For the nine patients with solitary brain metastases, which could not be analyzed by PET, we substituted the median value of the GLCM energy calculated on the remaining patients. A total of 14 patients were excluded for insufficient size of primary sites or metastases after contouring.

PET images obtained at diagnosis were analyzed by using the PETedge tool from MIM software to delineate the primary site and the largest metastatic sites. For metachronous disease, the primary site was delineated on a PET image taken before treatment, and the largest metastatic site was delineated on a separate PET image taken at the time the metachronous lesion was diagnosed. The co-occurrence matrix feature GLCM energy was extracted from both the primary sites and the metastases by using IBEX. The gray-level co-occurrence matrix was calculated in each CT image slice for the directions 0, 45, 90, and 135. The results from each slice and direction were combined to produce a single matrix from which the energy was extracted. The voxel intensities were discretized into 100 bins with ranges determined automatically from the images. Voxels were included in the matrix calculation if at least 50% of the voxel fell within the segmentation of the tumor [29].

Conventional prognostic factors

Sequential forward selection of the conventional prognostic factors (CPF) produced a baseline Cox proportional hazards [35–37] model comprised of primary tumor volume, gender, the number of metastases, and the presence of brain metastases. Though previously reported to be prognostic, the CPFs performance status, smoking status, histology, age at diagnosis, T category, N category, and synchronous vs. metachronous were not significant factors in our model [6–8,29,38–40]. Mutation status was not used for ALK due to insufficient positive results (n = 2). EGFR status was also unused due to reports of discordance between primary tumors and metastases [41,42]. All prognostic factors reported are from the time of diagnosis or, for patients with a metachronous metastasis, from the time of metachronous diagnosis. Performance status was gleaned from the medical record either from direct physician reports or from descriptions of functional status. Smoking status was considered as both number of pack years and as three levels: current smoker, past smoker, and never a smoker. The T category is a rating of the extent of the primary tumor. The N category reflects the extent of cancer within nearby lymph nodes. Each of these categories is part of the TNM staging system is most often used by doctors to stage cancer. It is maintained by AJCC (American Joint Committee on Cancer) and UICC (Union for International Cancer Control). OS was measured as the time from pathologic diagnosis of the primary site in synchronous disease (or the metastatic site in metachronous disease) until death in months. Patients not experiencing an event were censored at the last known follow-up date.

Statistical analysis

To assess the prognostic value of the energy QIFs, we added it to the clinical prognostic factor model (CPF model) to create two

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