Quantitative depth-based [^{18}F]FMCH-avid lesion profiling in prostate cancer treatment

Profilazione quantitativa di lesioni in pazienti affetti da cancro alla prostata tramite misure di profondità

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Abstract Besides prognostic clinical factors, baseline risk assessment in personalized cancer research would benefit from quantitative disease characterization to inform therapy planning. Texture analysis of [^{18}F]FMCH PET/CT imaging is paving the way for such purposes but its potential is still braked by radiomic feature limitation, such as redundancy and lack of standardization. In this work, we provide a method for a robust assessment of intratumor heterogeneity in patients affected by prostate cancer, through a depth-based ranking quantifying the level of centrality/outlyingness of the lesion with respect to peers. We interpret the results in terms of clinical information of lesions.

Abstract *La terapia personalizzata per malattie tumorali si basa sull'individuare fattori prognostici, mirati a incasellare i pazienti in classi di rischio: ad oggi, oltre a considerare parametri clinici e biologici, si punta a inserire l'analisi quantita-*

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tiva dei tessuti tumorali provenienti da dati di imaging, ad esempio la [^{18}F]FMCH PET/CT nel tumore alla prostata. La sfida è superare i problemi di ridondanza e standardizzazione che viziano questi dati non strutturati. Questo lavoro offre un metodo di valutazione robusta dell'eterogeneità intratumorale in ottica prognostica, tramite l'impiego di misure di profondità.

Key words: Depth Measures, Ranking, Radiomics, PET/CT medical imaging, Prostate cancer, Precision medicine

1 Contextual background

Prostate cancer is one of the leading causes of cancer death among men worldwide, with an estimate of over a million new cases of cancer and hundreds of thousands of deaths in 2018, a burden that is expected to grow in the upcoming years as population ages. Fortunately, death rate has been shown to have reduced in the past few years as extensive PSA-based screening programs have become available and been employed [1]. Indeed, treatment recommendation and risk factors currently relay upon patients' stratification, based on PSA, Gleason score, T-category which cluster men as low, intermediate and high risk patients who undergo increasingly aggressive treatments. Such therapies range from active surveillance to radiotherapy and radical prostatectomy.

Although most of the patients evolve well in long term [2], low-risk subjects may harbor more aggressive disease that remains undetected while resected patients may show occurrence of upgrading, upstaging or nodal metastases (i.e. biochemical progression). Consequently, risk stratification tools need to be improved and therapy pathways further optimized, in a personalized medicine fashion.

On the other hand, prostate cancer has been shown to exhibit spatial intratumor heterogeneity that can alter baseline risk assessment and behave as confounding factor in pre-treatment clinical-pathological prognosis [3]. Such knowledge could and should be exploited for improving treatment planning. Here comes the urge to assess and quantitively characterize intratumor heterogeneity in order to build an exhaustive representation of the disease. Indeed, the informed patient stratification will directly translate into improved patient treatments, wherein decisions regarding active surveillance or intensified therapy are made.

The role of [^{18}F]FMCH in patients with prostate cancer is well established, especially in ones with biochemical recurrence. Along with visual imaging inspection, the radiomic framework has spreaded in matter of quantitative PET/CT assessment, consisting on the extraction and evaluation of high dimensional advanced imaging features using high throughput methods [4]. Such features are referred as texture features and can be divided into conventional and higher-order parameters: more precisely, radiomic features include histogram-derived variables, shape-derived variables, GLCM matrix-derived variables, GLRLM matrix-derived variables, NGLDM matrix-derived variables and GLZLM matrix-derived variables. Each of these groups of variables is meant to capture distinct phenotypic differ-

ences of lesions resulting in quantitative measurements with potential prognostic power [5]]: lesions exhibiting similar radiomic profile are hypothesized to proxy similar physiologies and phenotypes, leading to similar outcomes. However, among radiomic features limitations, these variables suffer from redundancy and lack of standardization that prevent the radiomic workflow to significantly impact clinical practice.

In this work, we intend to propose a depth-based method for agnostic profiling of [^{18}F]FMCH-avid lesions in patients with recurrent prostate cancer, allowing a robust assessment of intratumor spatial heterogeneity. This could thus inform the yet unknown relationship between radiomic features and clinical outcomes, in terms of burden and biological aggressiveness.

2 Materials and Methods

92 patients (mean age 73 ± 7 years, median age 73 years, range 55-85) with multi-site, multi-lesion, recurrent prostate cancer have been retrospectively recruited (mean PSA at the time of [^{18}F]FMCH PET/CT 10,39 ng/ml) in the authors' institution. Clinical, biological and histology data as well as current treatment were recorded in all patients.

Whole-body PET/CT (GE Discovery ST) was acquired about 45 minutes after [^{18}F]FMCH (4 MBq/kg of body weight) administration. According to ISUP/WHO grading scale of prostate adenocarcinoma [6], patients were labeled as with mild and severe disease, having Gleason score ≤ 7 (n=53) and > 7 (n=31) respectively, except for 8 missing values.

A total of 370 lesions were found and classified according to TNM [14] in skeleton (n=221), distant lymph nodes (n=81) and regional lymph nodes (n=68). Lesions were semiautomatically segmented by experienced radiologists and radiomic texture features were extracted within regions of interest (lesions) using the LIFEx package (LIFEx website) [7]. Further statistical analysis has been implemented in R [8].

To overcome variable redundancy, the dataset was first filtered according to a correlation-based criterion. Specifically, Pearson pairwise correlation between radiomic variables were computed and highly correlated ($\geq$98%) variables were exclusively removed. No clinical rationale has been adopted in the choice of the variables to be kept, nevertheless attention has been payed to prefer conventional rather than higher-order variables for explainability reasons. Additionally, missing values of radiomic features have been filled according to median replacement rule. The resulting dataset variables has been standardized according to z-score method.

Data depths are a mathematical tool allowing for ranking multivariate objects, with respect to an underlying multivariate distribution [10]. They may be intended as the analogue of the quantiles for multivariate data: depth measures determine a centre-outward ordering of data points that are indeed geometrically ranked from the more central (median) to the more outsider (outlier) one [11].

Among data depths, several definitions are available in literature, such as Half-space (or Tukey) depth, Mahalanobis depth, Projection depth and Spatial depth. In

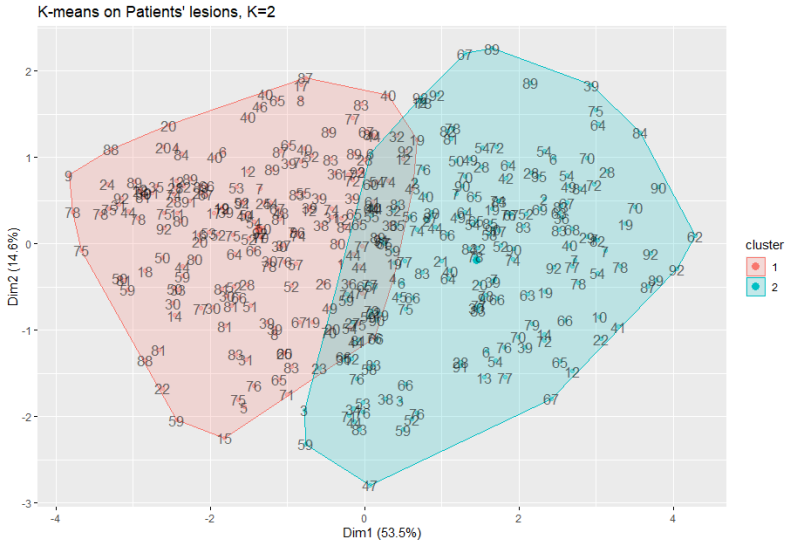

Fig. 1 Patients' lesions representation displayed in 2D latent space and labelled in two clusters.

the current analysis, Mahalanobis depth [9] is proposed as it leads to a *more spread out* distribution of points: in other words, the Mahalanobis depths distribution appears more dispersed about its center of symmetry than distributions stemming from other depths, leading to clearer results [12]. In this setting, Mahalanobis depth has been computed for each lesion, considering each group of radiomic variables separately. In this way, depth computation results in a variable reduction and transformation phase which allows to resume the 37 radiomic descriptors with 6 (one per semantic group of radiomic variables) agnostic ranking measures: indeed, the employment of a relative metric leads to overcome the lack of radiomic features standardization.

After that, the 370 6-dimensional vectors (one per lesion) were fed into a k-means clustering algorithm in order to find homogeneous classes of lesions, in an unsupervised setting. Optimal number of clusters was set equal to 2, according to exhaustive grid search implemented in [13]. Graphical inspection of such clusters is possible in Figure 1, where lesions, named with patient code, are plotted in 2D latent space and labelled in clusters. Evaluation was then performed in terms of clusters clinical characterization.

3 Results and Discussion

Kendall correlation coefficient was computed between each pair of the six depth measures, resulting in a 6x6 correlation matrix. According to Kendall, lesions appear not to show agreement between rankings: indeed, correlation coefficients are positive but never significant, with higher concordance for GLRLM and GLZLM depths, which show a correlation of 0.68. Being the depth of each lesion evalu-

ated for each radiomic group, the corresponding values depict the level of centrality of that lesion among the set of peers. Therefore, it is reasonable that concordance is not necessarily high for mainly two reasons: i) different radiomic groups capture different information about the lesion and the corresponding texture description, and ii) the lesion behaves differently over different descriptions provided by the groups. Therefore, such a dimensional reduction is able to globally capture different lesion's profiles, being agnostic in the way such diversity appears and may be evaluated. Ultimately, we end up with a six-dimensional depth vectors describing the radiomic lesion's profile (or fingerprint), and we focus on them in order to explore similarity patterns via unsupervised techniques. In fact, similar profiles were then grouped into homogeneous clusters, which can be interpreted as risk classes associated to different disease phenotypes and clinical outcomes. According to clusters characterization, as shown in table 1, membership to class 1 is coupled with no particular site, as 109 lesions can be found in skeleton and 81 in lymph nodes (36 distant + 45 regional); on the other hand, class 2 shows no prevalence for lesions to be in sites different from class 1 as well, with 112 of lesions being on skeleton and 68 on lymph nodes (45 distant + 23 regional). Of consequence, site may play a role in scoring disease severeness, however other factors may be further investigated to interpret the results.

For instance, along with lesion location, Standard Uptake Value (SUV) is assumed to differentiate malignant from benign processes. Correlated to conventional radiomic groups, SUV represents the lesion metabolic activity normalized over injected activity as highlighted by the tracer. Table 1 shows the number of lesions falling in the first $(-\infty,$-0.75], second (-0.75,-0.16], third (-0.16,0.58] and fourth $(0.58,\infty)$ SUV quartiles: accordingly, class 1 hosts lesions with SUV outlier values, since 125 lesions belong to first (59) and fourth (66) quartiles with respect to 65 lesions fitting in the second (32) and third (33) quartiles; on contrary, class 2 features lesions with SUV median values, as 119 lesions belong to second (60) and third (59) quartiles with the respect to 61 lesions fitting in the first (34) and fourth (27) quartiles. This assigns relevance to the tumor mutational burden, whose proxy is given by uptake values [16]: on one hand, average metabolically active lesions are labeled with class 2 risk score; on the other hand, both slightly and highly active lesions are given a distinct although unique risk score (class 1), as they might share higher-order descriptors' values.

Table 1 Characterization of clusters on the basis of clinical-physiological prognosticators.

	Lesions Site			**Lesions Standard Uptake Value (SUV)**			
	Regional Ln	Distant Ln	Skeleton	$(-\infty,$-0.75]	(-0.75,-0.16]	(-0.16,0.58]	$(0.58,\infty)$
Class 1	45	36	109	59	32	33	66
Class 2	23	45	112	34	60	59	27

4 Conclusion

Preliminary results showed that depth-based [^{18}F]FMCH-avid lesion profiling allows to overcome redundancy and lack of standardization issues in the radiomic framework. Such method could inform the investigation and the analysis of intratumor lesions heterogeneity, providing imaging biomarker for risk stratification to be proposed for a validation study to better characterize prostate cancer burden and biological aggressiveness, thus supporting imaging-based patients' treatment decision making.

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References

1. Klotz, Laurence, et al. "Long-term follow-up of a large active surveillance cohort of patients with prostate cancer." J Clin oncol 33.3 (2015): 272-277.
2. Hayes, Richard B., et al. "Dietary factors and risks for prostate cancer among blacks and whites in the United States." Cancer Epidemiology and Prevention Biomarkers 8.1 (1999): 25-34.
3. Sala, E., et al. "Unravelling tumour heterogeneity using next-generation imaging: radiomics, radiogenomics, and habitat imaging." Clinical radiology 72.1 (2017): 3-10.
4. Lambin, Philippe, et al. "Radiomics: extracting more information from medical images using advanced feature analysis." European journal of cancer 48.4 (2012): 441-446.
5. Aerts, Hugo JWL, et al. "Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach." Nature communications 5.1 (2014): 1-9.
6. Humphrey, Peter A. "Gleason grading and prognostic factors in carcinoma of the prostate." Modern pathology 17.3 (2004): 292-306.
7. Nioche, C., et al. "LIFEx: a freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity." Cancer research 78.16 (2018): 4786-4789.
8. Team, R. Core. "R: A language and environment for statistical computing." (2013): 201.
9. Pokotylo, Oleksii, Pavlo Mozharovskyi, and Rainer Dyckerhoff. "Depth and depth-based classification with R-package ddalpha." arXiv preprint arXiv:1608.04109 (2016).
10. Liu, Regina Y., Jesse M. Parelius, and Kesar Singh. "Multivariate analysis by data depth: descriptive statistics, graphics and inference,(with discussion and a rejoinder by liu and singh)." The annals of statistics 27.3 (1999): 783-858.
11. Dong, Ye, and Stephen MS Lee. "Depth functions as measures of representativeness." Statistical Papers 55.4 (2014): 1079-1105.
12. Bickel, Peter J., and Erich L. Lehmann. "Descriptive statistics for nonparametric models IV. Spread." Selected Works of EL Lehmann. Springer, Boston, MA, 2012. 519-526.
13. Charrad, Malika, et al. "Determining the best number of clusters in a data set." J Stat Softw. (2014).
14. Brierley, James D., Mary K. Gospodarowicz, and Christian Wittekind, eds. "TNM classification of malignant tumours." John Wiley and Sons, 2017.
15. Gunderson, Leonard L., and Joel E. Tepper. Clinical radiation oncology. Elsevier Health Sciences, 2015.
16. Jahromi, Amin Haghighat, et al. "Relationship between tumor mutational burden and maximum standardized uptake value in 2-[18 F] FDG PET (positron emission tomography) scan in cancer patients." EJNMMI research 10.1 (2020): 1-7.