FRI-290

Artificial intelligence assisted qFibrosis as a pathological “biomarker” to evaluate disease severity in patients with hepatocellular carcinoma

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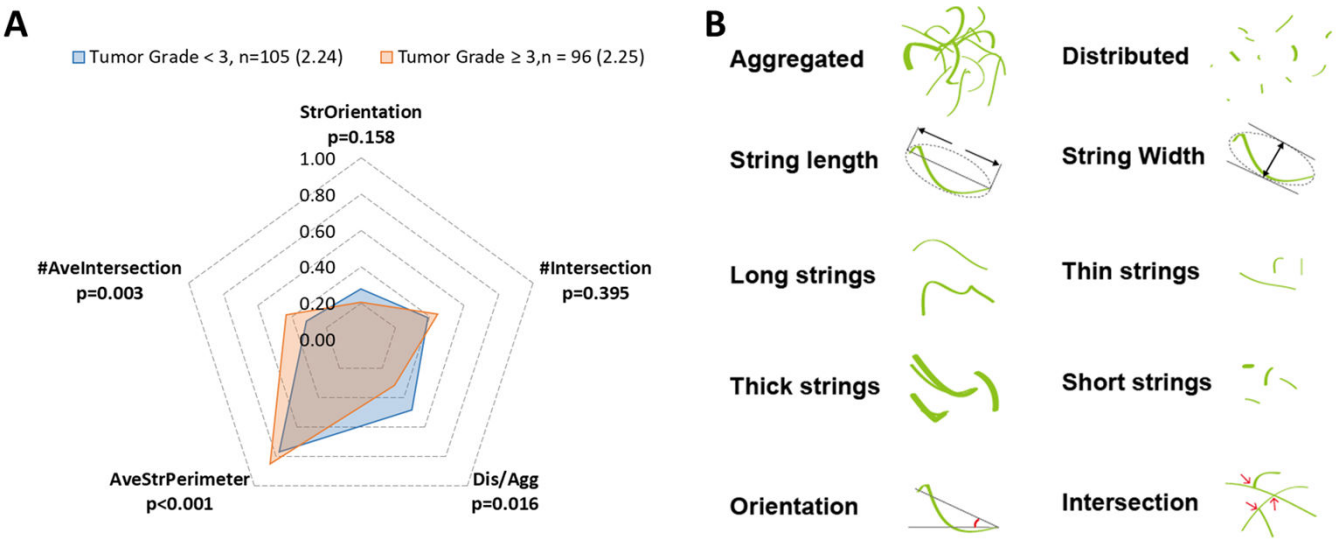
Background and Aims: Hepatocellular carcinoma (HCC) is highly heterogeneous in both intra-tumoral and inter-patient features and its manifestations in its pathology. Tumor grade is a comprehensive index that is subjectively judged by a pathologist, which does not reflect the local regional differences of tumor cells and different disease characteristics relating with its pathological heterogenicity. Our hypothesis is that collagen features of pathology in HCC analyzed by artificial intelligence assisted qFibrosis could be used as a pathological “biomarker” to evaluate disease severity.

Method: Tumor specimen from 201 patients with HCC who underwent curative treatment were scanned by the second harmonic generation (SHG) microscopy (HistoIndex Pte. Ltd., Singapore). Digital image analysis generated 33 collagen parameters. Patients were grouped into tumor grades ≤2 and tumor grades ≥3 groups. Collagen features of tumor specimen between the two groups were compared, and the features with most significant differences were selected. A combined index was built using the selected collagen features. The usefulness of the combine index to predict survival outcome and the correlation between the combine index and tumor grade were tested. Leave-one-out cross-validation method was utilized.

Results: Total of 5 collagen features has been selected by sequential selection methods to build a combine index model. In addition, the value of each collagen features is shown in the radar map (Figure A), so that the dynamics of the extracellular matrix can be visualized instead of just a single number, tumor grade. These collagen features are further illustrated (Figure B) to help researchers to visualize and investigate the histopathological relevance for further disease studies and treatment efficacy evaluations. With specific cut-off values, the combine index model was significant in distinguishing patients with tumor grades ≤2 and ≥3 ($P < 0.05$), as well as in distinguishing patients with long-term survival and early death ($P < 0.05$). Moreover, it can be seen in the radar map that the features that are relevant include intersections of collagen strings, ratio between distributed and aggregated collagens. This implies the physical characteristics of extracellular matrix (ECM) is correlated to long-term survival of the patients.

Conclusion: Pathological heterogenicity of HCC could be profiled by artificial intelligence assisted qFibrosis. Selected collagen features of HCC could be used as a pathological “biomarker” that has the potential to be a parameter to evaluate disease severity in patients with HCC. Quantitative measurements and the new visualization tools like radar map better reveals dynamic of ECM with other cell types, enhances disease studies and drug development programs in the future.

Figure: (A) Radar map showing 5 parameters: total orientation of strings (StrOrientation), total number o intersections (#Intersection), the ratio of distributed collagen area and aggregated collagen area (Dis/Agg), average perimeter for one string (AveStrPerimeter) and average number of intersections within each string
(B) graphical illustration of how colleagen strings are defined and measured


A
Tumor Grade < 3, n=105 (2.24)
Tumor Grade ≥ 3,n = 96 (2.25)
StrOrientation
p=0.158
1.00
0.80
0.60
0.40
0.20
0.00
#Intersection
p=0.395
Dis/Agg
p=0.016
AveStrPerimeter
p<0.001
#AveIntersection
p=0.003
B
Aggregated
Distributed
String length
String Width
Long strings
Thin strings
Thick strings
Short strings
Orientation
Intersection

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1 Introduction

- Hepatocellular carcinoma (HCC) is highly heterogeneous in both intra-tumoral and inter-patient features and its manifestations in its pathology.
- Tumor grade is a comprehensive index that is subjectively judged by a pathologist, which does not reflect the local regional differences of tumor cells and different disease characteristics relating with its pathological heterogenicity.

2 Aim

- Our hypothesis is that collagen features of pathology in HCC analyzed by artificial intelligence assisted qFibrosis could be used as a pathological "biomarker" to evaluate disease severity.

3 Method

- Tumor specimen from 201 patients with HCC who underwent curative treatment were scanned by the second harmonic generation (SHG) microscopy (HistoIndex Pte. Ltd., Singapore).
- Digital image analysis generated 33 collagen parameters.
- Patients were grouped into tumor grades ≤2 and tumor grades ≥3 groups. Collagen features of tumor specimen between the two groups were compared, and the features with most significant differences were selected.
- A combined index (T-index) was built using the selected collagen features.
- The usefulness of the combine index to predict survival outcome and the correlation between the combine index and tumor grade were tested.
- Leave-one-out cross-validation method was utilized.

4 Results

- Total of 5 collagen features has been selected by sequential selection methods to build a combine index model.
- In addition, the value of each collagen features is shown in the radar map (As shown in figure A in Figure.1), so that the dynamics of the extracellular matrix can be visualized instead of just a single number, tumor grade.
- These collagen features are further illustrated (As shown in figure B in Figure.1) to help researchers to visualize and investigate the histopathological relevance for further disease studies and treatment efficacy evaluations.
- Figure 2 shows the difference between SHG images with Tumor grade<3 and ≥ 3, AveStrPerimeter and #AveIntersection in a SHG image with Tumor grade ≥ 3 are larger than those in a SHG image with Tumor grade<3, while Dis/Agg is the opposite.
- With specific cut-off values, the combine index model was significant in distinguishing patients with tumor grades ≤2 and ≥3 ($P < 0.05$), as well as in distinguishing patients with long-term survival and early death ($P < 0.05$). (Figure 3)
- Moreover, it can be seen in the radar map that the features that are relevant include intersections of collagen strings, ratio between distributed and aggregated collagens.
- This implies the physical characteristics of extracellular matrix (ECM) is correlated to long-term survival of the patients.

Figure.1 (A) Radar map showing 5 parameters; (B) graphical illustration of how collagen strings are defined and measured

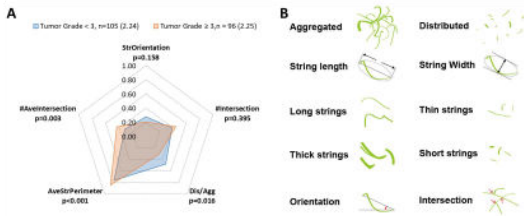
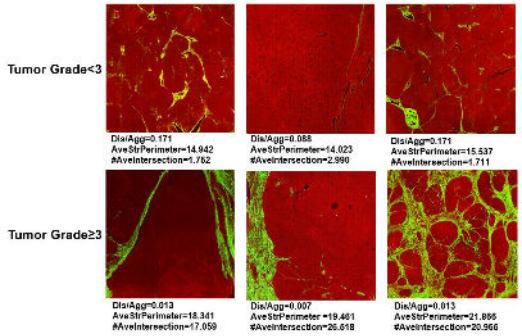


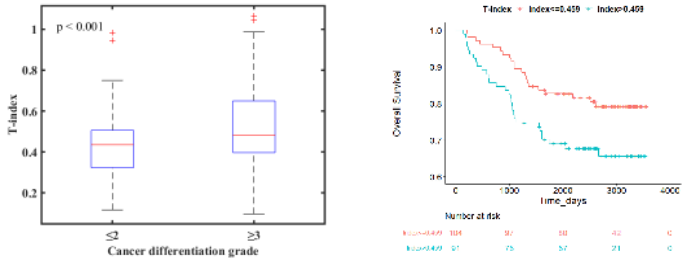
Figure.2 Examples of SHG images with showing 3 parameters with p<0.05 in radar map



5 Conclusions

- Pathological heterogenicity of HCC could be profiled by artificial intelligence assisted qFibrosis. Selected collagen features of HCC could be used as a pathological "biomarker" that has the potential to be a parameter to evaluate disease severity in patients with HCC.
- Quantitative measurements and the new visualization tools like radar map better reveals dynamic of ECM with other cell types, enhances disease studies and drug development programs in the future.

Figure. 3 (A) Performance of T-index for distinguishing cancer differentiation grades ≤2 and ≥3; (B) Kaplan-Meier analysis for overall survival



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