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Original Article

Correlation between Histogram Analysis Parameters Derived from DCE-MRI and the Expression of PD-L1 in Esophageal Squamous Cell Carcinoma. A Preliminary Study

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Abstract:

Purpose: To investigate the correlation between the histogram parameters (Ktrans, Kep, Ve) of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and programmed death-ligand 1 (PD-L1) expression in esophageal squamous cell carcinoma (ESCC).

Methods: Overall, 23 ESCC patients without prior surgery underwent DCE-MRI before treatment. Histogram parameters of DCE-MRI were extracted, and PD-L1 expression in lesions was detected by immunohistochemistry. PD-L1 expression was evaluated using three scoring methods: Tumor Proportion Score (TPS), Combined Positive Score (CPS), and Immune Cell Score (ICS).

Results: CPS correlated with the kurtosis and skewness coefficients derived from the Ktrans ($r = -0.416$, $p = 0.048$ and $r = -0.507$, $p = 0.013$). Additionally, CPS correlated with the P90 and kurtosis coefficients derived from the Kep ($r = 0.424$, $p = 0.044$ and $r = 0.422$, $p = 0.044$). ICS correlated with the mean value derived from the Ktrans ($r = 0.431$, $p = 0.040$). No association was observed between DCE-MRI parameters and TPS.

Conclusion: Ktrans and Kep related histogram analysis parameters derived from DCE-MRI showed correlation with PD-L1 expression in immune cells of ESCC. Therefore, histogram analysis parameters derived from DCE-MRI may serve as an effective imaging biomarker for pre-therapeutic assessment of immunotherapy eligibility in patients with ESCC.

Keywords: Esophageal squamous cell carcinoma; dynamic contrast-enhanced MRI; histogram; programmed death-ligand 1

1. Introduction

Surgery, radiotherapy, and chemotherapy are traditional treatment modalities for esophageal squamous cell carcinoma (ESCC)[1]. In recent years, with the widespread clinical application of immunotherapy, it has increasingly become one of the primary treatment options for patients with locally advanced unresectable or advanced esophageal cancer[2, 3].

Programmed death-ligand 1 (PD-L1)[4] is a transmembrane protein that highly expressed in various cells, including vascular, endothelial, immune, and tumor cells. PD-L1 expressed on tumor cell surfaces binds to PD-1 receptors on T cells directly affects the proliferation and function of immune cells involved in antitumor responses, thus high PD-L1 expression enables tumor cells to evade host immune surveillance[5]. immune checkpoint inhibitors (ICIs), Anti-PD-L1 monoclonal antibodies can block this pathway and restore T cell function. Studies have shown that [6, 7] combining immunotherapy with chemoradiotherapy enhances antitumor efficacy.

ICIs have demonstrated significant benefits in both preclinical and clinical settings for the treatment of esophageal squamous cell carcinoma (ESCC). Currently, immunotherapy has become a guideline-recommended standard second-line treatment for ESCC[8].

The abundance of PD-L1/PD-1 expression in tumor cells directly influences the efficacy of immunotherapy[9]. Pre-treatment assessment of PD-L1 levels in tumor tissue specimens and peripheral blood can help predict clinical efficacy. Traditional detection methods, such as RT-PCR (Reverse Transcription Polymerase Chain Reaction) and FISH (Fluorescence In Situ Hybridization), are technically complex, time-consuming, and costly. To address these limitations, researchers have explored imaging techniques, including CT, MRI and positron emission tomography (PET), for predicting immunotherapy response, with promising preliminary results[10]. However, clinical studies utilizing imaging-based quantification of PD-L1 expression to predict immunotherapy efficacy remain in their early stages. Studies have demonstrated that Dynamic contrast-enhanced MRI(DCE-MRI) can provide further accurate microstructural information of tumors[11, 12]. Therefore, imaging-based prediction of tumor histological characteristics, treatment response, and prognosis is feasible.

DCE-MRI can evaluate tumor morphological characteristics and detect intratumoral metabolic activity at the molecular level to assess biological behavior. The most commonly used quantitative parameters of this technique include: Ktrans (volume transfer constant), reflecting the diffusion rate of contrast agent from plasma through the vascular wall into the interstitial space; Kep (rate constant for contrast agent reflux from the extravascular extracellular space back to plasma); and Ve (extravascular extracellular volume fraction)[11, 13, 14]. Histogram analysis of perfusion parameters can characterize lesion heterogeneity based on the probability distribution of pixel values (mean, skewness, kurtosis, percentiles, etc.) for each parameter[14, 15]. Previous studies have demonstrated that histogram parameters of DCE-MRI can noninvasively evaluate key biological characteristics of malignant tumors including non-small cell lung cancer, breast cancer, and hepatocellular carcinoma, encompassing angiogenesis, neovasculari- zation, and proliferative potential[16-18]. However, according to current published reports, it remains unclear whether histogram parameters derived from DCE-MRI correlate with PD-L1 expression in ESCC. Therefore, This study aims to analyze the correlation between DCE-MRI histogram parameters and PD-L1 expression in ESCC, in order to comprehensively evaluate the feasibility and reliability of using multiparametric DCE-MRI histogram parameters for noninvasive prediction of PD-L1 expression in ESCC.

2. Materials and Methods

2.1.Patients

Overall, 23 ESCC patients treated at the Department of Radiation Oncology, the First Affiliated Hospital of Nanjing Medical University were involved in the study. The cohort included 15 males and 8 females with a median age of 63 years, range 51–78 years. All patients had a Karnofsky Performance Status (KPS) score ≥80 without comorbidities. DCE-MRI scans were performed after diagnosis but prior to any antitumor therapy. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University, and written informed consent was obtained from all participants.

2.2. DCE-MRI Scanning Protocol and Parameters

All examinations were performed using a 3.0T MRI scanner (MAGNETOM TrioTim; Siemens, Erlangen, Germany) with a 16-channel body coil. Prior to scanning, each patient underwent breathing and breath-holding training. The MRI sequences included: axial T1-weighted imaging (T1WI), axial and sagittal T2-weighted imaging (T2WI), and axial DCE-MRI sequence. The DCE-MRI protocol consisted of two parts: (1) pre-contrast scan using three flip angle sequences, and (2) dynamic contrast-enhanced sequence. For T1 mapping calculation, three flip angles (α=5°, 10°, 15°) were acquired using axial 3D volumetric interpolated breath-hold examination (VIBE) sequences with the following parameters: repetition time (TR) 5.22 ms; echo time (TE) 1.81 ms; field of view (FOV) 21×28 cm²; matrix size 256×138; slice thickness 3 mm. For dynamic contrast-enhanced MRI, gadodiamide (Omniscan, GE Healthcare; 0.5 mmol/mL) was administered

intravenously at a dose of 0.2 mL/kg body weight via power injector at a rate of 2.5 mL/s during the third phase of dynamic scanning, followed by a 15 mL saline flush at the same injection rate.

2.3. DCE-MRI Data Processing & Measurements

All DCE-MRI parameter measurements were performed by a radiologist with more than ten years of experience under double-blind conditions. All raw data from flip angle sequences and DCE-MRI sequences were saved in DICOM format, and the measurement and calculation of each parameter value were completed using the hemodynamic extended Tofts Liner two-compartment model in OmniKinetics software (GE Healthcare, China). Due to the influence of individual differences in cardiac output, vascular tension, and renal function on the arterial input function (AIF), this experiment used individualized user-AIF for parameter calculation[19, 20]. By referring to axial T2WI and T1WI enhanced images, regions of interest (ROI) were manually delineated to obtain DCE-MRI quantitative parameters: Ktrans refers to the rate constant for contrast agent diffusion from the intravascular space to the extravascular space; Kep refers to the rate constant for contrast agent reflux from the interstitial space back into the intravascular space after a certain time; Ve refers to the volume of the extravascular extracellular space. (The relationship between Ktrans, Kep and Ve can be expressed as: Ve = Ktrans/Kep). The histogram parameters of Ktrans, Kep, and Ve were calculated: mean, maximum, minimum, median, mode, 10th, 25th, 75th, and 90th percentiles, as well as Kurtosis coefficient and Skewness.

2.4. PD-L 1 Expression Analysis

Immunohistochemical staining was performed using the streptavidin-peroxidase (SP) method to detect PD-L1 expression in both tumor tissues and adjacent normal tissues. Two pathologists with over ten years of experience independently evaluated the PD-L1 staining results under double-blind conditions, and the average of their assessments was adopted.

PD-L1 expression was evaluated using three distinct scoring systems:

The evaluation of PD-L1 expression employs three standardized scoring methods: the Tumor Proportion Score (TPS) quantifies the percentage of tumor cells exhibiting partial or complete membrane staining at any intensity (both membrane and cytoplasmic staining are considered positive) to reflect PD-L1 expression in tumor cells; the Combined Positive Score (CPS) comprehensively assesses the sum of PD-L1-positive tumor cells and immune cells (including lymphocytes and macrophages) as a percentage of the total tumor cell count, providing a holistic view of the tumor microenvironment's immune status; the Immune Cell Score (ICS) specifically evaluates tumor-infiltrating immune cells by calculating the percentage of the tumor area occupied by PD-L1-stained immune cells, characterizing PD-L1 expression patterns in immune cells.

2.5. Statistical Analysis

Statistical analysis was performed using SPSS 23.0 software. Data are presented as mean ± standard deviation ($\bar{x} \pm s$). The normality of distribution was assessed using the Shapiro-Wilk test. Spearman's correlation coefficient (r) was used to evaluate the relationships between parameters. Comparisons between groups were analyzed using the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 The Histogram Parameters of Ktrans, Kep, and Ve in ESCC

The DCE-MRI histogram parameters (Ktrans, Kep, Ve) of the 23 patients are presented in Table 1. Figure 1 shows the histogram of calculated Ktrans, Kep, and Ve results from one representative ESCC patient.

3.2 PD-L1 Expression in ESCC

For the PD-L 1 expression of the TPS a mean value of 7.67±20.31 was identified. Furthermore, 17 patients (73.91%) showed no expression. For the PD-L 1 expression of the CPS a mean value of 10.60±15.37 was observed and in 15 patients (65.22%) no expression was found. For the PD-L 1 expression of the ICS a mean value of1.17±1.61 was found and 12 patients (52.17%) had no expression.

3.3 Correlations between DCE-MRI derived Histogram Parameters and PD-L1 Expression

For the associations between histogram parameters derived from DCE-MRI and the PD-L 1-expression, some statistically significant correlations were found.

The Kurtosis and Skewness coefficients derived from Ktrans showed correlations with PD-L1 expression of the CPS (r = -0.416, p = 0.048 and r = -0.507, p = 0.013). The P90 and Kurtosis coefficients derived from Kep were correlated with PD-L1 expression of the CPS (r = 0.424, p = 0.044 and r = 0.422, p = 0.044). The mean value derived from Ktrans demonstrated correlation with PD-L1 expression of the ICS (r = 0.431, p = 0.040). None of the DCE-MRI parameters showed statistically significant associations with PD-L1 expression of the TPS.

Table 1 summarizes the investigated histogram parameters derived from DCE-MRI.

Parameter		Mean ± Standard Deviation	Range
Ktrans(1/min)	Mean	0.19±0.13	0.05-0.55
	Min	0.07±0.04	0.01 -0.17
	Max	0.65±0.58	0.07-2.42
	P10	0.12±0.08	0.05-0.28
	P25	0.16±0.13	0.07-0.61
	P75	0.27±0.21	0.06-0.68
	P90	0.33±0.17	0.11-0.84
	Median	0.20±0.13	0.05-0.52
	Mode	0.17±0.16	0.04-0.55
	Kurtosis	6.81±10.19	0.32-32.89
	Skewness	1.20±1.06	-0.24-3.69
Kep(1/min)	Mean	0.43±0.26	0.09-0.82
	Min	0.08±0.05	0.02-0.21
	Max	1.08±0.70	0.12-2.95
	P10	0.20±0.12	0.06-0.57
	P25	0.29±0.20	0.07-0.76
	P75	0.51±0.35	0.05-1.21
	P90	0.61±0.37	0.09-1.28
	Median	0.42±0.21	0.13-0.94
	Mode	0.36±0.27	0.07-0.86
	Kurtosis	5.21±6.73	0.25-22.90
	Skewness	0.67±0.65	-0.11-2.34
Ve(unitless)	Mean	0.48±0.17	0.18-0.86
	Min	0.13±0.09	0.02-0.38
	Max	0.89±0.23	0.35-1.26
	P10	0.30±0.18	0.07-0.66
	P25	0.36±0.17	0.15-0.85
	P75	0.62±0.24	0.15-1.13
	P90	0.73±0.22	0.22-1.09
	Median	0.46±0.17	0.19-0.82
	Mode	0.40±0.23	0.07-0.82
	Kurtosis	2.15±1.96	-0.46-5.97
	Skewness	0.43±0.54	-0.74-1.32

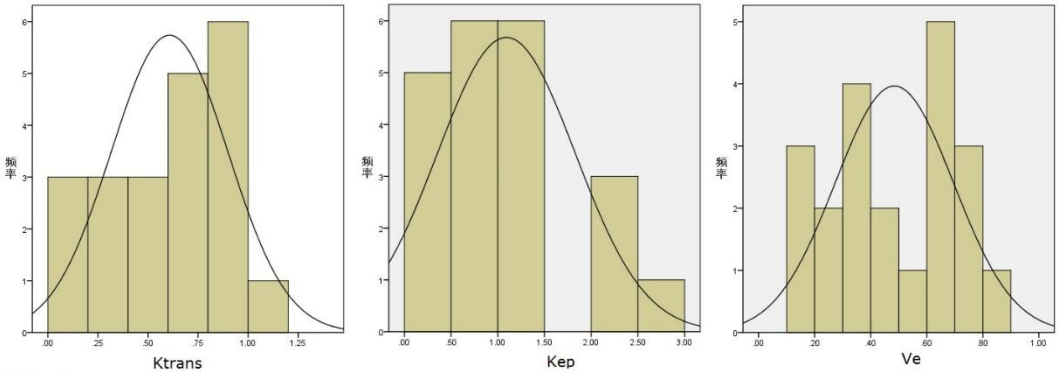

Figure 1. Parametric histogram analysis of Ktrans, Kep, and Ve in the same patient.

4. Discussion

Esophageal carcinoma remains one of the most prevalent malignancies worldwide. Despite significant therapeutic advancements through improved surgical techniques, refined radiotherapy protocols, and targeted drug development, the prognosis remains poor with persistently high mortality rates. Current literature reports a dismal 5-year survival rate of merely 15-25%[1, 21].

PD-1/PD-L1 are key negative regulatory molecules in the immune checkpoint pathway, playing a central role in tumor immune evasion. Overexpression of PD-L1 on tumor cell surfaces can specifically bind to PD-1 receptors on tumor-infiltrating lymphocytes(TILs).This interaction transmits immunosuppressive signals that significantly inhibit T cell migration, proliferative activity, and the secretion of cytotoxic mediators (such as perforin and granzymes)[3, 9]. This mechanism not only induces T cell exhaustion but also substantially impairs their tumor-killing effects, thereby promoting immune evasion.

PD-L1 expression levels show a significant correlation with immunotherapy efficacy. In this study, three clinically validated scoring methods: Tumor Proportion Score (TPS), Combined Positive Score (CPS), and Immune Cell Score (ICS) were employed to evaluate PD-L1 expression in tumor tissues. Among the 23 ESCC patients enrolled, the positivity rates were 60.87% for TPS and 69.92% for ICS. Consistent with previous findings, most ICS-positive tumors in this cohort also demonstrated TPS positivity. Current evidence demonstrates that elevated PD-L1 expression in tumor cells(ESCC, lung cancer, etc) frequently correlates with poor prognosis, tumor recurrence/metastasis, and angiogenesis[22, 23].

DCE-MRI represents a non-invasive diagnostic modality that integrates both morphological and hemodynamic assessments. This technique has demonstrated clinical utility not only for tumor diagnosis but also for evaluating tumor progression, metastatic potential, and prognosis[10-12].Recent studies have shown that in head and neck squamous cell carcinomas [24] and breast cancer[17], PD-L1 positive scores are correlated with Ktrans and Kep parameters. Therefore, DCE-MRI histogram parameters may be effective imaging indicators for pre-evaluating whether cancer patients can receive immunotherapy. The technique's ability to quantify tumor microvascular characteristics potentially reflects the underlying tumor immune microenvironment. These findings suggest that multiparametric DCE-MRI analysis may serve as a promising imaging biomarker for predicting immunotherapy responsiveness.

Ktrans, Kep, and Ve are commonly used quantitative kinetic parameters of DCE-MRI that can provide information about tumor biology. Histogram analysis of tumors offers more quantitative indicators beyond mean values, objectively reflecting tumor heterogeneity with high reproducibility and consistency[25, 26]. Consequently, histogram parameters derived from DCE-MRI can more objectively represent the tumor microenvironment, particularly microvessel density in tumor tissue. Studies demonstrate that Ktrans strongly correlates with vascular endothelial growth factor and can be used for precise evaluation of therapeutic efficacy of molecularly targeted drugs against tumor vascular endothelial growth factor receptors[12]. Parameters derived from the rate constant (Kep) correlate

with vascular density[27]. Additionally, research has found that MRI parameters Ktrans and Kep show positive correlation with the proliferation index Ki-67 expression in breast cancer[28], enabling prediction of tumor proliferative potential. Parameters derived from the extracellular extravascular volume ratio (Ve) are sufficiently sensitive to reflect cellularity in tissues.

The correlation analysis in this study demonstrated statistically associations between DCE-MRI histogram parameters and PD-L1 expression patterns. The Ktrans-derived Kurtosis and Skewness coefficients were associated with PD-L1 expression of the CPS ($p<0.05$), as were the Kep-derived P90 and Kurtosis coefficients ($p<0.05$). The Ktrans mean value also showed association with ICS scores. No significant associations were observed between DCE-MRI parameters and PD-L1 TPS expression. These findings suggest that DCE-MRI histogram analysis may serve as a potential imaging biomarker for evaluating tumor immune microenvironment characteristics. As mentioned previously[23], most patients with ESCC exhibit high PD-1/PD-L1 positivity rates in tumor tissues, with expression levels showing correlations with clinicopathological characteristics and prognosis. PD-L1 expression positively correlates with both microvessel density and microlymphatic density[29], suggesting its involvement in ESCC angiogenesis, partially explains the current study's results. Interestingly, in one study , no statistically significant difference in treatment response rates between PD-L1 negative and positive patients when evaluating tumor cells alone; however, incorporating tumor-associated immune cells revealed significant intergroup differences[30]. Our results further demonstrate significant heterogeneity among different PD-L1 scoring systems, a phenomenon warranting clinical attention. The Immune Cell Score (ICS) specifically quantifies PD-L1-positive immune cells within the tumor microenvironment without reflecting tumor cell PD-L1 expression.

DCE-MRI histogram parameters showed meaningful correlations with both ICS and CPS scores but not with TPS. This suggests that dynamic contrast-enhanced MRI (DCE-MRI) may more comprehensively characterize PD-L1-positive immune microenvironments compared to assessing PD-L1-positive tumor cells alone. Nevertheless, these findings require validation through large-scale clinical studies to determine their potential translational applications.

The results of this study provide a reliable basis for non-invasive evaluation, but there are still many issues to be resolved. For example, the relatively long time required for DCE-MRI examination limits its clinical application, resulting in a small number of enrolled patients that may introduce some errors. Additionally, although the region of interest delineation was independently completed by different physicians during the study, the inherent subjectivity in the delineation process inevitably leads to further measurement errors.

5. Conclusion

In conclusion, the multiparametric histogram parameters of DCE-MRI show correlation with PD-L1 TPS scores in esophageal cancer patients who have not undergone surgery, providing direction for further research on the feasibility of non-invasive methods to predict PD-L1 expression in esophageal cancer.

Author Contributions

JY wrote the paper. LW made important revisions to the paper. DY collected the literature. DML approved the final version of the paper for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal connections that could influence the work reported in this article.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethics Committee of First Affiliated Hospital of Nanjing Medical University(NO.2024-SR-938). The patients/ participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Data Availability Statement

All information in this case is included in this published article. Further inquiries can be directed

to the corresponding author.

Reference

1. CHEN Y, YU R, LIU Y. Combine radiotherapy and immunotherapy in esophageal squamous cell carcinoma [J]. Critical reviews in oncology/hematology, 2023, 190: 104115.
2. HANG Y, LI Z, HUANG Y, et al. Advancements in immunotherapy for advanced esophageal squamous cell carcinoma: a comprehensive review of current strategies and future directions [J]. Expert review of clinical immunology, 2024, 20(8): 971-84.
3. SU X, LI J, XU X, et al. Strategies to enhance the therapeutic efficacy of anti-PD-1 antibody, anti-PD-L1 antibody and anti-CTLA-4 antibody in cancer therapy [J]. Journal of translational medicine, 2024, 22(1): 751.
4. IMAI H, KAIRA K, KAGAMU H. Advanced Research on Immune Checkpoint Inhibitor Therapy [J]. Journal of clinical medicine, 2022, 11(18).
5. HAYASHI H, NAKAGAWA K. Combination therapy with PD-1 or PD-L1 inhibitors for cancer [J]. International journal of clinical oncology, 2020, 25(5): 818-30.
6. YAP T A, PARKES E E, PENG W, et al. Development of Immunotherapy Combination Strategies in Cancer [J]. Cancer Discov, 2021, 11(6): 1368-97.
7. SALAS-BENITO D, PéREZ-GRACIA J L, PONZ-SARVISé M, et al. Paradigms on Immunotherapy Combinations with Chemotherapy [J]. Cancer Discov, 2021, 11(6): 1353-67.
8. WATERS J K, REZNIK S I. Update on Management of Squamous Cell Esophageal Cancer [J]. Current oncology reports, 2022, 24(3): 375-85.
9. TANG Q, CHEN Y, LI X, et al. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers [J]. Frontiers in immunology, 2022, 13: 964442.
10. BERA K, VELCHETI V, MADABHUSHI A. Novel Quantitative Imaging for Predicting Response to Therapy: Techniques and Clinical Applications [J]. American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting, 2018, 38(38): 1008-18.
11. WINFIELD J M, PAYNE G S, WELLER A, et al. DCE-MRI, DW-MRI, and MRS in Cancer: Challenges and Advantages of Implementing Qualitative and Quantitative Multi-parametric Imaging in the Clinic [J]. Topics in magnetic resonance imaging : TMRI, 2016, 25(5): 245-54.
12. FLIEDNER F P, ENGEL T B, EL-ALI H H, et al. Diffusion weighted magnetic resonance imaging (DW-MRI) as a non-invasive, tissue cellularity marker to monitor cancer treatment response [J]. BMC cancer, 2020, 20(1): 134.
13. GARCíA-FIGUEIRAS R, BALEATO-GONZáLEZ S, PADHANI A R, et al. How clinical imaging can assess cancer biology [J]. Insights into imaging, 2019, 10(1): 28.
14. LI X, HUANG W, HOLMES J H. Dynamic Contrast-Enhanced (DCE) MRI [J]. Magnetic resonance imaging clinics of North America, 2024, 32(1): 47-61.
15. PETRALIA G, SUMMERS P E, AGOSTINI A, et al. Dynamic contrast-enhanced MRI in oncology: how we do it [J]. La Radiologia medica, 2020, 125(12): 1288-300.
16. MESSANA G, BORTOLOTTO C, THULASI SEETHA S, et al. Non-invasive PD-L1 stratification in non-small cell lung cancer using dynamic contrast-enhanced MRI [J]. European radiology, 2025.
17. WU Z, LIN Q, WANG H, et al. Intratumoral and Peritumoral Radiomics Based on Preoperative MRI for Evaluation of Programmed Cell Death Ligand-1 Expression in Breast Cancer [J]. Journal of magnetic resonance imaging : JMRI, 2024, 60(2): 588-99.
18. GONG X Q, LIU N, TAO Y Y, et al. Radiomics models based on multisequence MRI for predicting PD-1/PD-L1 expression in hepatocellular carcinoma [J]. Scientific reports, 2023, 13(1): 7710.
19. TSENG C H, NAGTEGAAL M A, VAN OSCH M J P, et al. Arterial input function estimation compensating for inflow and partial voluming in dynamic contrast-enhanced MRI [J]. NMR in biomedicine, 2024, 37(12): e5225.
20. TSENG C H, JASPERS J, ROMERO A M, et al. Improved reliability of perfusion estimation in dynamic susceptibility contrast MRI by using the arterial input function from dynamic contrast enhanced MRI [J]. NMR in biomedicine, 2024, 37(1): e5038.
21. SHEIKH M, ROSHANDEL G, MCCORMACK V, et al. Current Status and Future Prospects for Esophageal Cancer [J]. Cancers, 2023, 15(3).

22. DENG H, ZHAO Y, CAI X, et al. PD-L1 expression and Tumor mutation burden as Pathological response biomarkers of Neoadjuvant immunotherapy for Early-stage Non-small cell lung cancer: A systematic review and meta-analysis [J]. Critical reviews in oncology/hematology, 2022, 170: 103582.
23. YAP D W T, LEONE A G, WONG N Z H, et al. Effectiveness of Immune Checkpoint Inhibitors in Patients With Advanced Esophageal Squamous Cell Carcinoma: A Meta-analysis Including Low PD-L1 Subgroups [J]. JAMA oncology, 2023, 9(2): 215-24.
24. MEYER H J, HöHN A K, SUROV A. Associations between histogram analysis parameters derived from dynamic-contrast enhanced MRI and PD L1-expression in head and neck squamous cell carcinomas. A preliminary study [J]. Magnetic resonance imaging, 2020,72:117-21.
25. JING J, MEKHANIK A, SCHELLENBERG M, et al. Combination of deep learning reconstruction and quantification for dynamic contrast-enhanced (DCE) MRI [J]. Magnetic resonance imaging, 2025, 117: 110310.
26. PADHANI A R, LIU G, KOH D M, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations [J]. Neoplasia (New York, NY), 2009,11(2):102-25.
27. HOFFMANN E, MASTHOFF M, KUNZ W G, et al. Multiparametric MRI for characterization of the tumour microenvironment [J]. Nature reviews Clinical oncology, 2024, 21(6): 428-48.
28. UNCU U Y, AYDIN AKSU S. Correlation of Perfusion Metrics with Ki-67 Proliferation Index and Axillary Involvement as a Prognostic Marker in Breast Carcinoma Cases: A Dynamic Contrast-Enhanced Perfusion MRI Study [J]. Diagnostics (Basel, Switzerland), 2023,13(20).
29. BABA Y, NOMOTO D, OKADOME K, et al. Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma [J]. Cancer science, 2020, 111(9): 3132-41.
30. CHOW L Q M, HADDAD R, GUPTA S, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort [J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2016, 34(32): 3838-45.