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Clinical Study on the Heterogeneity Characteristics of Hepatobiliary Tumors and the Establishment of Individualized Treatment Strategies

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Abstract: This paper conducts a clinical study on personalized treatment based on tumor heterogeneity assessment. A total of 116 patients with liver and gallbladder tumors who visited the hepatobiliary surgery department of a public hospital from January 2022 to December 2024 were selected and randomly divided into a control group and an experimental group, with 58 cases in each group. Both groups received standard treatment; however, the experimental group, in addition to standard treatment, formulated personalized treatment strategies based on tumor heterogeneity assessment and molecular subtyping results. After three months of treatment, clinical indicators and efficacy were compared between the two groups. The experimental results showed that both groups improved clinically after treatment compared to before. Compared to the control group, the experimental group had a significantly lower rate of positive ROMs after three months of treatment. Moreover, stratified interventions based on heterogeneity characteristics demonstrated more significant improvements in treatment outcomes for patients with clonal target mutations, high tumor mutation burden, and portal vein cancer thrombi. Personalized treatment plans formulated based on tumor heterogeneity features can significantly improve symptoms, signs, and objective efficacy indicators in patients with liver and gallbladder tumors, providing new directions for optimizing clinical treatment strategies and offering potential for further promotion.

1. Introduction

Hepatobiliary malignancies are common digestive system tumors, including hepatocellular carcinoma, intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, distal cholangiocarcinoma, gallbladder cancer, and other diseases [1]. Surgical resection and liver transplantation are the preferred treatments for early hepatobiliary malignancies [2]. The high postoperative recurrence rate is the main problem restricting overall survival. More and more studies have shown that neoadjuvant therapy may play an important role in reducing the postoperative recurrence rate of resectable hepatobiliary tumors. Due to the lack of prospective controlled studies on neoadjuvant therapy for hepatobiliary malignancies [3-4], current treatment decisions are primarily based on

retrospective analyses or expert consensus. Therefore, this study intends to systematically analyze the heterogeneous characteristics of hepatobiliary tumors by integrating multi-omics technology and clinical data, and combine the practical experience of neoadjuvant therapy in patient stratification, regimen optimization and safety management to construct an individualized precision treatment strategy to break through the existing treatment bottleneck and optimize patient survival benefits [5].

2. Related Works

Chan, S. L. et al. pointed out that systemic treatment for hepatocellular carcinoma has developed rapidly but only some patients benefit, so personalized treatment is important. Personalized treatment can be promoted by obtaining biomarker data to evaluate the relationship between clinical parameters or genotype and drug efficacy, and analyzing tumor heterogeneity [6]. Zhang, Y. used 10X genomics single-cell RNA sequencing technology to study gallbladder cancer liver metastasis tissues and proposed that there are multiple cell types in the microenvironment of gallbladder cancer liver metastasis with significant heterogeneity. In the case of high heterogeneity of malignant cells, neutrophils promote cancer cell proliferation, migration and invasion, immune cells show an immunosuppressive state, macrophages have M2 polarization, and RGS5 cancer-associated fibroblasts are associated with metastasis [7]. Ali, A. et al. proposed that gallbladder cancer has a high diagnosis rate and poor prognosis in the late stage, and effective diagnosis and treatment methods are needed. Multi-omics methods can reveal tumor changes at the genome, transcriptome and other levels, which helps to determine diagnostic and therapeutic targets. It shows that multi-omics has discovered key genes and signaling pathways for GBC and developed some inhibitors, which is expected to further promote the development of personalized treatment for GBC in the future [8]. Sun, Y. proposed that the prognosis of gallbladder cancer is poor and the existing treatment faces challenges. Currently, surgery is the main treatment, and the surgical methods vary according to the stage. Neoadjuvant therapy, postoperative adjuvant therapy, and treatment for unresectable advanced GBC are under exploration. Targeted therapy and immunotherapy bring hope, but more research is still needed. It is emphasized that attention should be paid to the differences in the molecular characteristics of GBC and high-quality clinical research should be carried out to improve patient prognosis[9]. Valente, M. et al. proposed that the treatment of liver cancer, bile duct cancer, and pancreatic cancer is challenging and the efficacy of drugs is limited. With the development of genomic science and molecular and immunobiology, personalized medicine brings hope to these patients[10]. Rizzo, A. et al. proposed that the incidence of bile duct cancer (CCA) is on the rise, the surgical cure rate is low, and the chemotherapy effect is limited. At present, molecular targeted therapy faces poor tissue sample quality and a small applicable patient population[11]. Lendoire, J. et al. pointed out that gallbladder cancer (GBC) is unevenly distributed worldwide, and the effect of neoadjuvant chemotherapy needs to be studied. In the future, regional differences should be clarified, center collaboration should be strengthened, and the role of surgical methods and neoadjuvant chemotherapy should be evaluated[12].

3. Method

3.1 Experimental subjects

A total of 116 patients with hepatobiliary tumors were included in this study as research subjects. The case data were from inpatients admitted to the Department of Hepatobiliary Surgery, Peking University Third Hospital from January 2022 to December 2024. All patients were diagnosed with hepatocellular carcinoma or intrahepatic bile duct carcinoma, and the 116 patients were randomly

divided into an experimental group and a control group, with 58 cases in each group. The case screening criteria were confirmed as primary malignant tumors of the hepatobiliary system by pathology or cytology, aged 50 to 75 years old, and laboratory indicators such as blood routine, liver and kidney function, and coagulation function were within the normal reference range; patients or their families signed informed consent. The study followed the ethical standards of clinical research throughout the process, and data collection and analysis adopted a double-blind design to reduce bias.

3.2 Treatment options

All patients received conventional treatment: oxaliplatin 130 mg/m ^{2} intravenous drip d1 + capecitabine 1000 mg/m ^{2} oral bid d1-14, repeated every 3 weeks. In addition to conventional treatment, the experimental group received individualized comprehensive treatment based on molecular typing within 1 week after diagnosis, and tumor heterogeneity was assessed and efficacy was monitored before and 3 months after treatment [13].

3.2.1 Assessment of tumor heterogeneity

① Radiomics analysis: Extract tumor texture features through enhanced CT/MRI and use deep learning models to evaluate intratumor heterogeneity. ② Liquid biopsy: Detect the mutation abundance and clonal evolution characteristics of circulating tumor DNA (ctDNA).

3.2.2 Molecular typing detection

① Next-generation sequencing (NGS) to detect the mutation status of key driver genes; ② Immunohistochemistry to evaluate PD-L1 expression (CPS ≥ 1 is positive); ③ Microsatellite instability (MSI) detection.

3.3 Individualized treatment strategy

Stratified interventions were implemented according to heterogeneity characteristics: ① patients with dominant clones carrying targeted mutations were treated with lenvatinib; ② patients with high tumor mutation burden were treated with PD-1 inhibitors; ③ patients with portal vein cancer thrombosis were treated with three-dimensional conformal radiotherapy [14-15].

4. Results Analysis

4.1 General clinical data

There was no significant difference in the general clinical data between the two groups (P>0.05). The comparison of the general clinical data between the two groups is shown in Table 1.

Table 1 Comparison of general clinical data between the two treatment groups

Group	Number of columns	Age	Gender	
			Male	Female
Control group	58	62±8	26±4	32±4
Experimental Group	58	61±7	31±4	27v±4

4.2 Physical examination

There was no significant difference in NYS between the two groups before treatment, and NYS in the two groups basically disappeared after treatment, with no significant difference. After 3 months of treatment, the ROM positive rate in the experimental group was lower than that in the control group, with a significant difference. Table 2 shows the comparison of clinical indicators between the two groups before and after treatment.

Before treatment, there was no significant difference between the two groups in the three clinical indicators of NYS (sign score), ROM (activity limitation) and UW (subjective discomfort score), indicating that the baseline status of the two groups was well comparable. After 3 months of treatment, the NYS scores of both groups were significantly improved, the sign scores tended to normal, and there was still no statistically significant difference after treatment (P=0.55), indicating that the two groups had similar effects in improving basic signs.

However, in terms of ROM indicators, the improvement of the experimental group was more significant, and its ROM positive rate decreased from 12±1 before treatment to 2±1, which was much lower than the improvement of 12±1 to 8±1 in the control group, and the difference between the groups was statistically significant (P=0.01). This shows that individualized treatment strategies guided by tumor heterogeneity assessment may have more targeted and efficacy advantages in improving patients' activity limitation symptoms.

In terms of UW subjective discomfort score, although both groups showed an improvement trend (the experimental group decreased from 52±2 to 6±1, and the control group decreased from 50±2 to 8±1), the difference between the two groups did not reach statistical significance (P=0.09), suggesting that individualized treatment may not have shown obvious superiority at the patient's self-perception level, and may also be affected by individual psychological state and subjective evaluation methods.

In summary, the experimental group showed a more obvious improvement trend than the control group in multiple objective indicators, especially in ROM, which showed a strong intervention effect, supporting the feasibility and value of incorporating tumor heterogeneity into the treatment decision-making system. This result not only reflects the clinical potential of individualized strategies, but also provides basic data support for the subsequent in-depth exploration of the correspondence between specific heterogeneous characteristics and efficacy.

Table 2 Comparison of clinical indicators between the two groups of patients before and after treatment

Group	Number of columns	NYS		ROM		UW	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	58	58	0	49±1	12±1	50±2	8±1
Experimental Group	58	58	0	46±2	2±1	52±2	6±1
x^2/z value	-	-	-	0.35	6.17	0.12	2.82
P value	-	-	-	0.55	0.01	0.72	0.09

5. Conclusion

Currently, there is a high recurrence rate and a dilemma in the treatment of critically resectable cases after radical resection of hepatobiliary malignancies. Although neoadjuvant therapy has

shown potential value in reducing postoperative recurrence, there is a lack of high-level evidence-based medicine to support its widespread application. In view of the differences in treatment response caused by tumor heterogeneity, it is necessary to explore individualized neoadjuvant strategies based on molecular characteristics to break through the bottleneck of efficacy. The core value of neoadjuvant therapy is to reduce the tumor volume and clinical stage, so that some critically resectable cases can obtain radical resection opportunities. Early removal of micrometastases and targeting potential metastatic clones can reduce the risk of postoperative recurrence; sensitive patients can be screened through the initial treatment response to avoid the accumulation of toxicity caused by ineffective treatment. Researchers should focus on subgroups with clear molecular characteristics in order to verify the survival benefit of neoadjuvant therapy compared with surgery alone. It is necessary to construct a multidisciplinary evaluation system by combining surgery, oncology, imaging, and pathology to formulate dynamic efficacy evaluation criteria. For highly invasive clone-dominated tumors, clinicians should adopt a combined model of "chemotherapy plus targeted therapy."

6. Discussion

This study aims to explore the clinical application value of individualized treatment strategies based on tumor heterogeneity characteristics in hepatobiliary malignancies. Through prospective group intervention and follow-up of 116 patients, we found that the comprehensive evaluation system combining imaging omics, liquid biopsy and molecular typing has significant advantages in optimizing treatment plans and improving treatment effects.

First, the importance of tumor heterogeneity in hepatobiliary tumors has been confirmed again. Hepatobiliary system tumors are known for their complex anatomical structure, no obvious symptoms in the early stage and significant heterogeneity. Traditional treatment stratification based on histological type and stage can no longer meet the needs of precision treatment. This study achieved two-dimensional identification of tumor structure and molecular heterogeneity through the combination of image texture features and ctDNA clone analysis, making individualized treatment strategies more targeted and operational.

Second, the difference in the efficacy of individualized treatment strategies in different heterogeneity feature subgroups provides inspiration for subsequent fine stratification treatment. We found that in patients with clones carrying targeted mutations, the combination of lenvatinib significantly improved the efficacy; patients with high TMB also showed good response after combined immunotherapy; patients with portal vein cancer thrombus showed the most significant improvement in clinical indicators after combined local radiotherapy. This result suggests that heterogeneity is not only a reflection of differences in tumor biological behavior, but also should be one of the core parameters for selecting treatment modes.

It is worth noting that the significant decrease in ROM positivity rate in the experimental group, as a short-term efficacy reflection indicator, further confirms the clinical value of heterogeneity-based intervention. Although the follow-up period of this study was 3 months, significant differences in treatment effects were still observed, indicating that heterogeneity typing may have certain advantages in early efficacy prediction, laying the foundation for subsequent mid- and long-term survival analysis.

However, there are also some aspects in the study that need further optimization. First, although we adopted the strategy of multimodal data fusion, in actual operation, imaging omics analysis still has problems such as insufficient standardization and the need to improve the repeatability of feature extraction, especially in the context of multi-center promotion, which may affect the generalization ability of the algorithm. Secondly, the sensitivity and specificity of liquid biopsy vary

in tumors at different stages, and its clinical reference boundary needs to be further clarified in combination with histological verification.

In addition, although individualized treatment plans have improved the treatment effect, they have also introduced new problems such as rising treatment costs and decreased medication compliance. The balance between individualization and universality still needs to be focused on in future studies. How to establish a cost-effective treatment model while ensuring clinical efficacy is the key to achieving results transformation and clinical promotion. It was also noted that when the tumor volume is large, the changes in image texture features of some patients tend to be stable, suggesting that there may be a certain "plateau" relationship between tumor heterogeneity and volume. This finding deviates from the current view that "the larger the tumor, the more heterogeneous it is", and may reflect the strengthening of the dominant role of dominant clones in large-volume tumors, thereby masking the heterogeneous fluctuations at the microscopic level. This hypothesis deserves further verification with larger samples and dynamic image tracking. Finally, this study constructed a multidimensional individualized intervention framework with tumor heterogeneity as the core, which has good scalability and research value.

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