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Enteron

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Atezolizumab plus bevacizumab improves survival outcomes vs. sorafenib in unresectable HCC

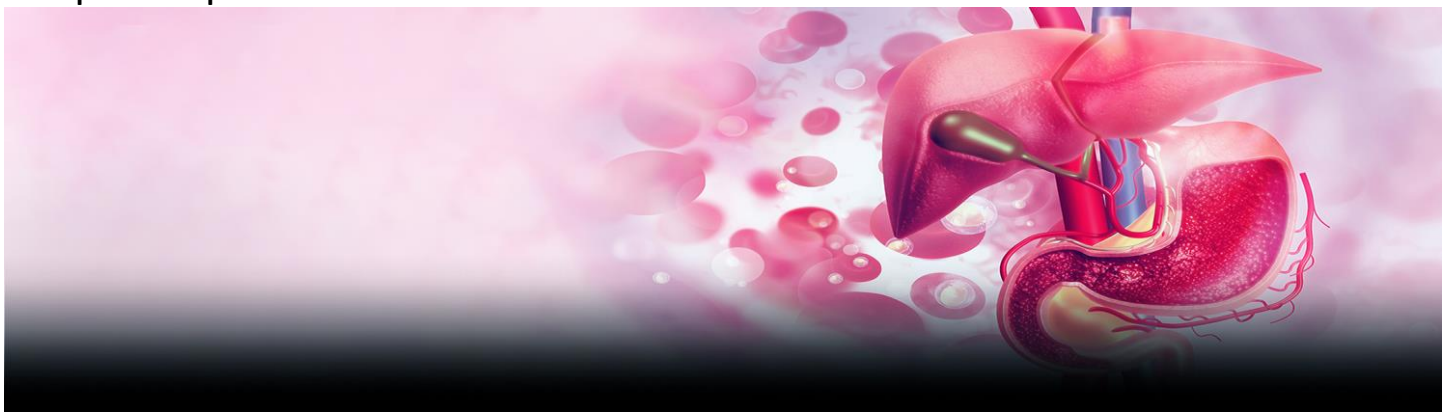
According to randomized phase 3 trial IMbrave150 reported in The New England Journal of Medicine, atezolizumab in conjunction with bevacizumab enhanced OS and PFS compared with sorafenib in patients with unresectable hepatocellular carcinoma.

Richard S. Finn, MD, Medicine Professor in the Department of Medicine, Hematology / Oncology Section, at the David Geffen School of Medicine, University of California, LA said the advanced HCC has a bad prognosis, and while conditions have changed in the last several years with some new product approvals, there has been little change in first-line OS for more than 12 years.

Sorafenib, which historically proven to be safer than placebo, is normal medication for patients like these. Lenvatinib has recently been licensed for demonstrating non-inferiority to sorafenib. After it was licensed no preventive treatment has been found to boost the OS vs. sorafenib.

HCC is a leading global source of cancer-related death. Early stage cancer may be treated through resection, transplantation of the liver, or ablation. Nonetheless, people with unresectable later-stage disease have weak prognosis. The development and progression of liver cancer has been linked to several active pathways of intrinsic immune evasion including VEGF overexpression. Anti-VEGF drugs, such as bevacizumab, also shown a capacity inside the tumor and its microenvironment to the the VEGF-mediated immunosuppression.

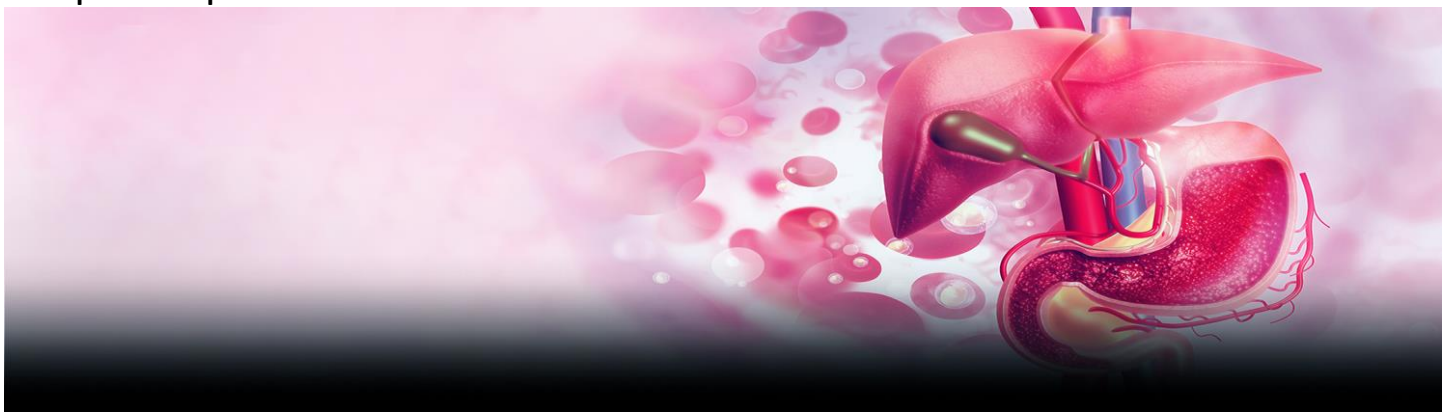
There was interest in bevacizumab as a single agent in HCC over a decade ago but the studies had mixed efficacy and safety results and never moved beyond phase 2. Immunotherapy has been of concern in HCC. Nivolumab, pembrolizumab and ipilimumab are all accepted as second-line alternatives based on phase 2 results, in conjunction with nivolumab.



In HCC, many specific immunotherapies are being researched which target the PD-L1 / PD-1 pathway. These include atezolizumab, which targets PD-L1 specifically to inhibit contact with PD-1 and B7-1 and to reverse repression of T-cells. An earlier phase 1b analysis demonstrated atezolizumab in patients with unresectable HCC coupled with bevacizumab mediated antitumor action.

In a broader sample, Finn and collaborators were trying to determine the protection and efficacy of atezolizumab + bevacizumab. The study involved 501 unresectable HCC patients who had no previous medical therapy. In tandem with bevacizumab (n=336), or sorafenib (n=165), researchers allocated patients 2:1 to atezolizumab. Treatment persisted until health gain became unacceptably harmful or lost.

Source: Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382:1894-1905



Relationship of PPAR activity and outcome of patients resected for hepatocellular carcinoma

INTRODUCTION

Local ablation, surgical resection, or transplantation can cure the hepatocellular carcinoma (HCC). There are still restricted therapeutic choices for patients with advanced stage HCC (macrovascular interference or metastatic spread). Chemotherapy with the Sorafenib protein kinase inhibitor results in significant adverse events, and only increases overall survival by a 2.8-month mean. In a phase 1/2 trial, therapy with the PD-1 inhibitor Nivolimab resulted in reaction levels of 15 to 20 percent and follow-up studies are pending.

In most cases, HCC diagnosis is based entirely on imaging with a multiphase computer tomography (CT) scan, and there are only a few clinically relevant biomarkers available that assess prognosis. The most commonly used is alpha fetoprotein (AFP), which can allow a difference (AFP>20 ng / ml) between 62% and 90.2% respectively, cirrhosis and HCC with sensitivity and specificity. So, HCC can still be present in several patients with usual AFP. Peroxisome-activated receptors (PPARs) are ligand-dependent nuclear receptors that control lipid metabolism, among other processes. Their primary action mechanism is the transduction of metabolic and nutritional signals via transcriptional responses. There are three known PPAR isoforms, with overlapping yet distinct transcriptional targets. PPAR In Rodents

Regulation contributes to enlargement of the kidney, steatosis and carcinogenesis. However, humans remain immune to these PPAR activation results. This may be attributed to a comparatively 10 times smaller level of PPAR present in human livers compared to rodents. However, a recent analysis in 804 patients found a link between low expression of PPAR, compared with Immunohistochemistry, and longevity shorter. PPARs therefore allow ligands to be triggered and aligned with transcriptional cofactors. Therefore, transcriptome analysis of known PPAR target may be a better readout of PPAR transcriptional activity.

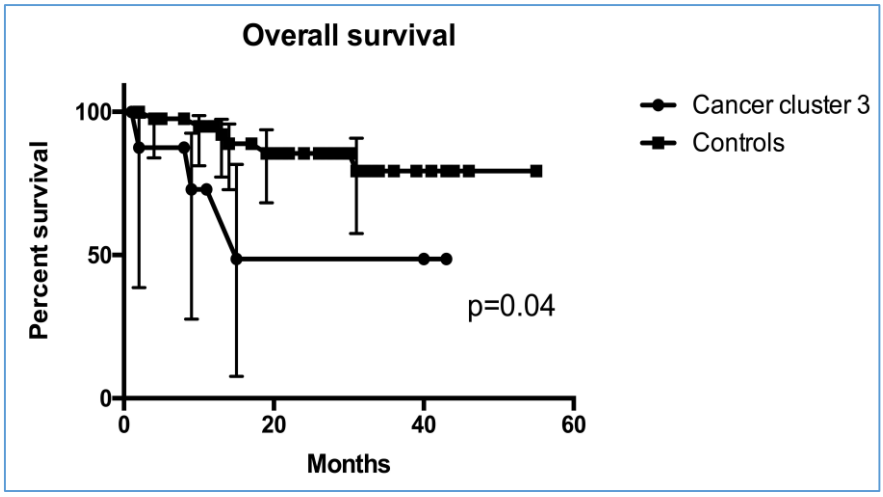
The aim of this analysis was to investigate the RNA sequencing the association between PPAR development and ALDH7A1 expression in tumor and related nontumor liver tissue from the same patients and their connection to recovery, recurrence and histological parameters in HCC surgical resection patients.

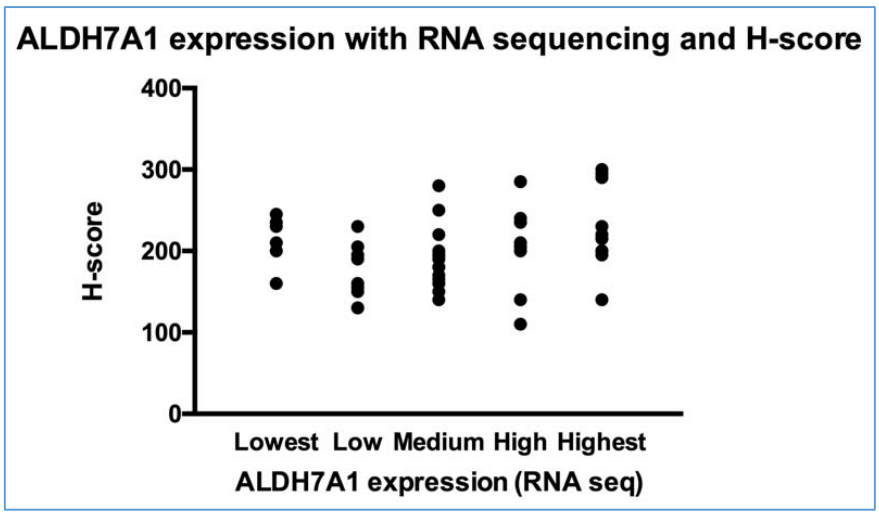
METHODS

We included patients undergoing liver resection for HCC at a tertiary referral center for hepatopancreato- biliary surgery between May 2014 and January 2018. PPAR activity and ALDH7A1 expression were evaluated by RNA sequencing and correlated with overall survival, recurrence and histological features.

RESULTS

We included 52 patients with a median follow-up of 20.9 months, predominantly males (88.5 %) with a single tumor (84.6 %) in a non-cirrhotic liver (73.1 %). Three-year overall survival was 48.6 % in patients with a specific PPAR target gene expression profile (cancer cluster 3) compared with 81.7 % in controls (p=0.04, Log rank test). This remained significant (odds ratio 14.02, 95 % confidence interval 1.92-102.22, p=0.009) when adjusted for age, cirrhosis, microvascular invasion, number of tumors and free resection margins. ALDH7A1 expression was not correlated with PPAR or any outcomes.





CONCLUSION

In conclusion, the analysis showed that tumor sample PPAR development was correlated with worse prognosis for patients undergoing HCC liver resection. PPAR target signature can be a valuable biomarker for predicting poor prognosis and may theoretically serve as a medical care guide, however more studies are required

REFERENCES

Pommergaard HC, Hasselby JP, Willemoe GL, et al. Peroxisome proliferator-activated receptor activity correlates with poor survival in patients resected for hepatocellular carcinoma [published online ahead of print, 2020 May 2]. J Hepatobiliary Pancreat Sci. 2020;10.1002/jhbp.745.

A propensity score-matched analysis of long term Outcomes of Gastric peroral endoscopic pyloromyotomy versus gastric electrical stimulation in the treatment of refractory gastroparesis

INTRODUCTION

Gastroparesis is a persistent pathological stomach motility condition, and a disease marked by impaired gastric emptying without any functional obstruction. Gastroparesis medication pharmacotherapy is also not very successful, with fewer than one percent of patients receiving prescription care reporting significant progress after one year or more. But gastroparesis diagnosis remains very difficult. Gastric electrical stimulation (GES) has been developed as a medicinally refractory gastroparesis treatment method.

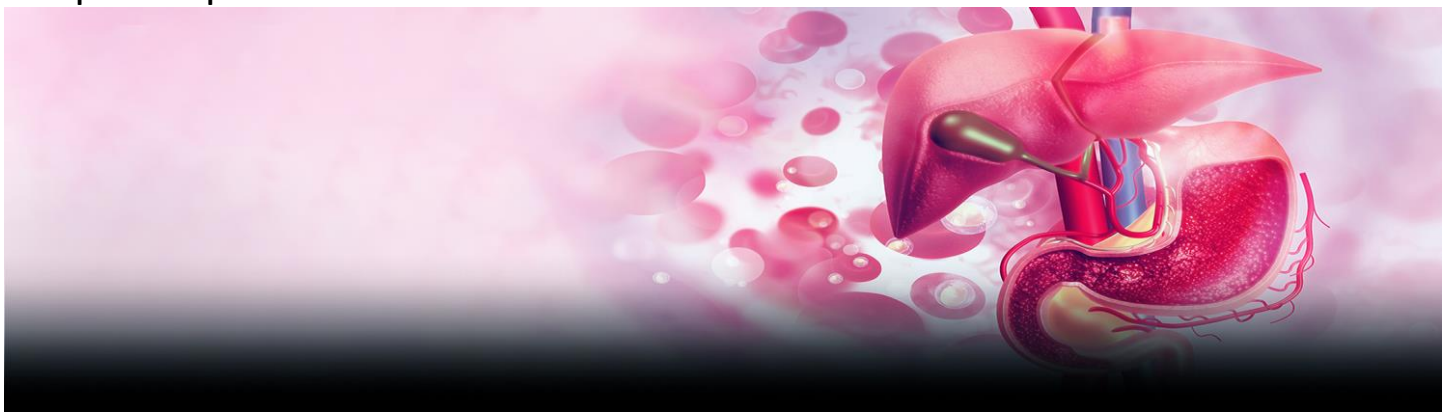
Many open-label trials recorded 1-year therapeutic response levels ranging from 45% to 74%, with just a quarter of the initial patients sustaining 3-year response. This intrusive technique can be compounded by discomfort, inflammation, dislocation and skin deterioration at the implantation site and is correlated with a removal rate of 6.3 percent-12.8 percent Gastric peroral endoscopic pyloromyotomy (G-POEM), often named peroral pyloromyotomy, is becoming a popular therapeutic choice for refractory gastroparesis as a pyloric-directed intervention and a less painful procedure. Several trials found that G-POEM culminated in a therapeutic response rate of 57% – 85% over one year. G-POEM 's effectiveness was also found for patients where GES fell. Despite the positive findings and less intrusive design of G-POEM, we proposed that G-POEM will be preferable to GES in the care of refractory gastroparesis patients. This study was conducted to compare the long term effectiveness of G-POEM with that of GES in patients with refractory gastroparesis.

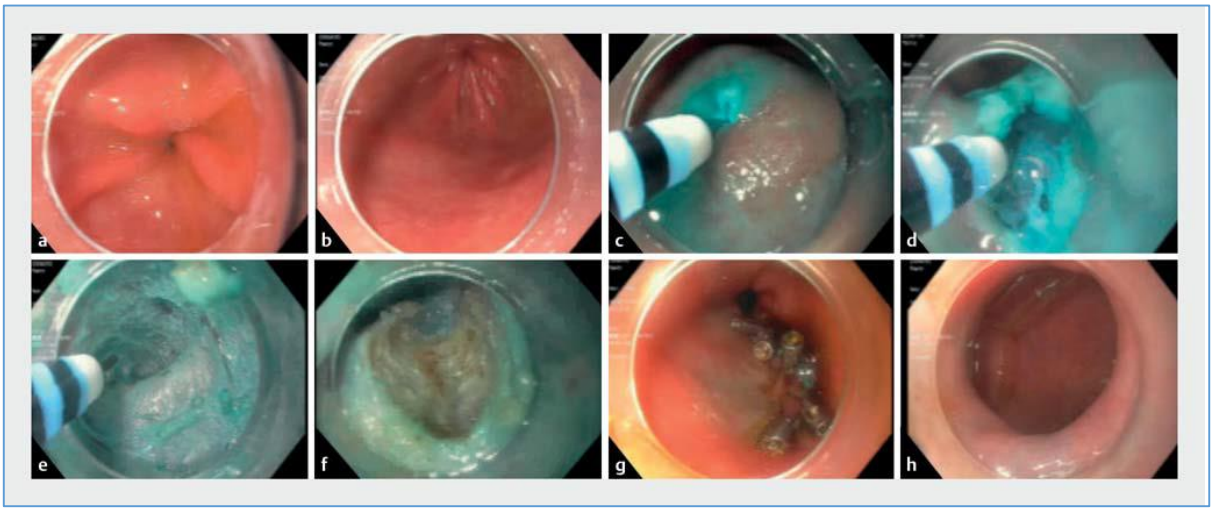
METHODS

We retrospectively evaluated 111 consecutive patients with refractory gastroparesis between January 2009 and August 2018. To overcome selection bias, we used propensity score matching (1:1) between G-POEM and GES treatment. The primary outcome was the duration of clinical response.

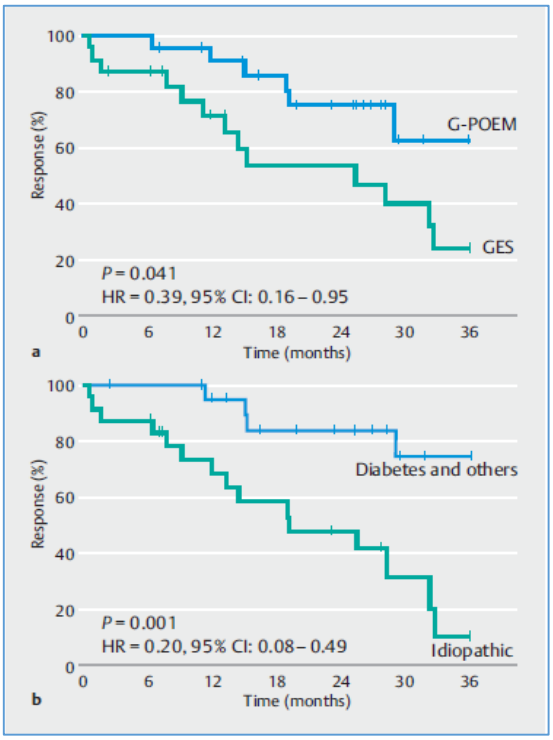
RESULTS

After propensity score matching, 23 patients were included in each group. After a median follow-up of 27.7 months, G-POEM had a significantly better and longer clinical response than GES (hazard ratio [HR] for clinical recurrence 0.39, 95% confidence interval [CI] 0.16 – 0.95; P = 0.04). The median duration of response was 25.4 months (95%CI 8.7 – 42.0) in the GES group and was not reached in the G-POEM group. The Kaplan – Meier estimate of 24- month clinical response rate was 76.6% with G-POEM vs. 53.7% with GES. GES appeared to have little effect on idiopathic gastroparesis (HR for recurrence with G-POEM vs. GES 0.35, 95 %CI 0.13 – 0.95; P = 0.05). The incidence of adverse events was higher in the GES group (26.1% vs. 4.3 %; P = 0.10).

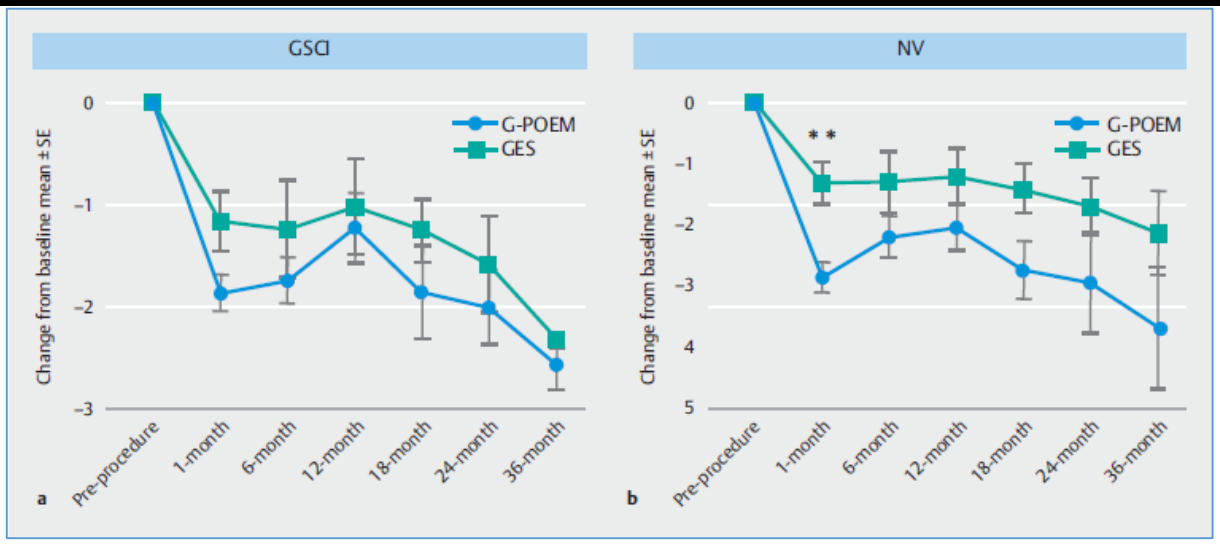




Steps in the gastric peroral endoscopic pyloromyotomy (G-POEM) procedure. a Pylorus before G-POEM. b Antrum. c Antrum mucosal lifting and incision. d Submucosal tunneling. e Pyloric ring inside submucosal tunnel. f Myotomy. g Endoclips to close the incision. h Pylorus after G-POEM.



Cumulative rate of response among patients with refractory gastroparesis. a Response between gastric peroral endoscopic pyloromyotomy (G-POEM) and gastric electrical stimulation (GES) groups. b Response according to etiology. HR, hazard ratio.



Changes from baseline to month 36 by treatment group. a Gastroparesis Cardinal Symptom Index. b Nausea and vomiting scores. GES, gastric electrical stimulation; G-POEM, gastric peroral endoscopic pyloromyotomy; SE, standard error. **P < 0.01.

CONCLUSION

These results indicate that patients with refractory gastroparesis who obtained treatment with G-POEM had better long-term therapeutic responses compared with patients who received treatment with GES. In patients with idiopathic gastroparesis, the positive outcomes with GPOEM are likely to derive from the superior clinical response. GES has had a higher adverse event rate than G-POEM. There clearly needs to be more studies in this area.

REFERENCES

Shen S, Luo H, Vachaparambil C, et al. Gastric peroral endoscopic pyloromyotomy versus gastric electrical stimulation in the treatment of refractory gastroparesis: a propensity score-matched analysis of long term outcomes. Endoscopy. 2020;52(5):349-358.