

been specified how ototoxicity in the AHEP0731 study was measured (eg, with pure tone audiometry) and how many patients were actually tested for it, which would be helpful to understand what the true proportion of ototoxicity was with this relatively small cisplatin dose.

Another interesting observation of the COG AHEP0731 trial regards the prolonged return (over 6 months) of serum α -fetoprotein concentrations to normal concentrations in a substantial proportion of patients (five [11%] of 46 patients). Only 25 (54%) patients normalised α -fetoprotein concentrations by the end of chemotherapy. It is also unclear why two additional patients never normalised α -fetoprotein concentrations, and it would be interesting to know what happened to them. For example, was this situation associated with the presence of additional liver pathology?

A source of concern is the fact that three neoplastic events were associated either with positive PRETEXT annotation factors, such as tumour rupture, or the presence of the small-cell undifferentiated tumour histological variant.⁴ Tumour rupture seems to be associated with worse prognosis, at least in the context of the CHIC analysis, and in the recent SIOPEL studies,^{5,6} patients with tumour rupture were considered to be high-risk and received intense preoperative chemotherapy. It seems that, on the contrary to tumour rupture, microscopic residuum did not seem to affect the patients' outcome in this trial, which is in line with the recent SIOPEL study⁷ classifying patients with post-resection microscopic residual disease that did not adversely influence the patients' outcome.

It is unusual that in this trial, as many as 20 patients had positive annotation factors (vascular involvement; or involvement of portal vein, hepatic veins, or inferior vena cava, or a combination). Seven of these patients were positive for both factors and might have been operated outside official trial recommendations. These observations call for caution about the inclusion of patients with positive PRETEXT annotation factors (vascular involvement or tumour rupture) in the low-risk hepatoblastoma group. Additionally, two patients classified as PRETEXT group III

for tumour extent should have been considered ineligible for upfront resection. These observations raise the problem of insufficient adherence to surgical resection guidelines offered by the AHEP0731 study, which clearly counselled against upfront resection in patients with positive PRETEXT annotation factors. Unfortunately, in most centres worldwide, the decision on whether a tumour is initially resectable stems mostly from the experience of the surgeon and not from objective assessment, clearly showing the inherent problem of all past and upcoming new hepatoblastoma studies.

How can we standardise and determine the value of surgical intervention, either immediate or delayed, for these patients? How can we plan surgery in an objective and comparable manner? Without addressing these issues, it will be difficult to decide which patients benefit the most from immediate surgery and in which cases it should be avoided.

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First steps to regulate advertising of areca nut in China

The areca nut is the fruit of the areca palm (*Areca catechu*), which mainly grows in Hainan province in China. Areca nut is sometimes referred to as betel

nut because betel leaves are often used to wrap it, but in China it is generally chewed without betel leaves. Although the areca nut has long been considered





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an independent major risk factor for oral cancer, the government of China has not regulated its use.^{1,2}

On March 7, 2019, the Hunan Provincial Areca Nut Food Industry Association issued a notice on stopping advertising,³ announcing that all areca nut companies in the Hunan province had been requested to stop any form of advertising of their products in the province.^{4,5} Yang Xun, president of the Hunan Province Areca Nut Food Industry Association, publicly confirmed the news.³

In traditional Chinese medicine, areca nut is recommended for improving digestion, strengthening the body, and maintaining good health. There is a proverb in Hunan—*areca nut and smoke, mana is boundless; areca nut and wine, get everything you want; areca nut, smoke, and wine, live to ninety-nine*. However, it is well known that the International Agency for Research on Cancer confirmed in 2004 that even without any additives areca nut can cause oral cancer, and areca nut was added to the list of group 1 carcinogens.⁶

Hunan province has a high incidence of oral cancer. A retrospective study including the records of 8222 patients with oral cancer in Hunan province between 2005 and 2016 suggested that more than 90% of these cancers seemed to be related to areca nut use.²

In Hunan province, there is a huge vested interest in the areca nut industry, which sustains the economy of the area, as well as strong traditions and cultural links to this product, which might explain why the Chinese government has been reluctant to recognise areca nut as a carcinogen. Without governmental regulation, areca nut advertising is laissez-faire and the areca nut industry sponsorship of well known television programmes is growing.

On Feb 16, 2019, the Ministry of Public Health of China presented the Healthy Oral Action Program (2019–2025), which focuses on the long-term oral health consequences of chewing areca nut and proposes targeted education and oral health examinations to promote early diagnosis and treatment of periodontal disease in areas where chewing areca nut is common.⁷ Under the pressure of the Ministry of Public Health of China, the Hunan Province Areca Nut Food Industry Association issued the notice on stopping advertising³ on March 7, 2019,

stating that all enterprises from now on must stop all domestic advertising and the work must be completed by March 15, 2019. For enterprises that fail to fulfil the requirements of this notice, the market management department will collect evidence and take corresponding measures.³ Unfortunately, to date the official website of the Hunan Betel Food Industry Association still advocates the idea of the healthy areca nut.⁸

We believe that this ban on advertising is just the first step in a much needed, wider ban on areca nut in the future, which will inevitably affect the livelihood of farmers who plant areca nut in the Hainan province and will affect an industry that generates tens of billions of dollars in the Hunan province. However, moving away from false health benefit claims and not allowing industry to mislead the public is only the beginning. We sincerely hope that the Chinese Government will recognise the scientific evidence showing that areca is not a miracle medicinal nut as soon as possible and alert people to the fact that it is actually harmful to health.

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