December 23, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6961-review.doc).

Title: An update on imaging of Peutz-Jeghers Syndrome

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6961

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

Thank you very much for your nice comments

Reviewer 2

Thank you very much for your interesting and valuable comments.

We have answered your suggestions as follows:

- We now give more details about the age at which the different complications of the conditions tend to arise, and the malignant potential at different ages, as follows:

" Many patients will develop gastrointestinal polyps during their childhood or adolescence; the median time to first presentation is around 11-13 years, and half of PJS patients will have experienced symptoms by the age of 20[1, 8]. During this time, transient intussusception, small-bowel obstruction and bleeding are common complications. The median age of intussusception is 15 years but with wide variability (range:

3.7-45.4 years)[8]. In Hinds's series dealing with the impact of pediatric screening on the complications of childhood PJS, approximately 30% of the PJS patients required laparotomy before the age of 10 and 68% before the age of 18[9]. Seventy percent of the initial laparotomies were performed urgently for intestinal obstruction[9]." inserted page 4 of the chapter 'Clinical Features'.

"*PJS patients have an increased risk for gastrointestinal and non-gastrointestinal cancer. A meta-analysis has found that the cumulative risk of developing cancer in PJS patients aged between 15 and 64 years, ranging between 37% and 93%[3]. Malignancy most commonly occurs within the small-bowel, with a median age at diagnosis of 41 years[2]. The risk of colorectal cancer is 3%, 5%, 15% and 39% at the ages of 40, 50, 60 and 70 respectively. Upper gastrointestinal cancers are less common, as the average age for stomach cancer diagnosis is 30[2].*

The increased risk of extra-intestinal malignancy is largely due to breast and gynecological cancers in women along with pancreatic cancer, particularly in men[1]. The overall cumulative risk for cancer has been estimated at over 76% in PJS patients and is higher in females than in males, with a risk of breast cancer similar to that of women with BRCA1 or BRCA2 mutations[2, 3]. The cumulative breast cancer risk is estimated between 31-54% at age 60, with a mean diagnosis age of 37. The earliest documented case of breast cancer in PJS was at 19 years of age[4]. The risk of pancreatic cancer is unclear; it varies between 7% and 36% by the age of 60[2,4].

In his study, Giardello et al. reported a risk of cervical cancer of 9% by the age of 64, with a mean age at diagnosis of 34 and a risk of 10% for uterine cancer. Giardello also calculated a 21% lifetime risk of ovarian tumors[1]. Testicular cancer surveillance is also recommended. In a review of the literature, all testicular cancers were Sertoli cell tumors, with a mean age of occurrence of 9 and a range of 3-20 years[1]. The prevalence of thyroid and lung cancers is also slightly increased in PJS but screening for these types of cancer has not been validated[4]." inserted in page 4 in the chapter 'Clinical features'.

- We added details concerning the evidence for the effectiveness of screening in reducing the frequency of complications from polyps and cancer, as follow:

"*Most authors agree that surveillance is needed in PJS patients but there is no consensus as to which organs should be monitored, with what frequency they should be monitored, and at what age surveillance should begin[2, 5, 9, 17, 18]. One study suggests that polyps < 10 mm require the monitoring of the small bowel, although those recommendations are based on data of insufficient quality[13]. Nevertheless, the guidelines in Beggs' recent article, produced by a group of European experts, suggest baseline surveillance with esophagogastroduodenoscopy at the age of 8, colonoscopy every 1-2 years after the age of 50, and videocapsule endoscopy (VCE) at 8-10 years of age and then every two to three subsequent years or earlier*

if any abdominal symptoms are present[4]. For extra-intestinal malignancies, Giardello recommends a monthly breast self-examination starting at the age of 18 years and a semiannual clinical breast examination and annual mammography or MRI starting at the age of 25 years[1]. However, Beggs et al. suggest that annual MRI/ultrasound surveillance should start at age 25-30 years, substituted with mammography after the age of 50. Routine surveillance for pancreatic cancer has not been proven to be beneficial, but MRI or ultrasonography beginning at the age of 30 years has been proposed[1,3,4]. Beggs also recommends a regular screening consisting of 2-3 yearly cervical smears using liquid based cytology from age 25. The Giardello and Van Lier studies also recommend an annual transvaginal ultrasound and CA-125 screening for ovarian cancer beginning at age 25[1,3,4]. Annual testicular examination by testicular ultrasound is recommended in patients where abnormality is detected[4].

These studies emphasize that the surveillance of PJS patients may prolong life expectancy and improve outcomes through the early detection of carcinomas. Gender and age-specific cancer surveillance are important considerations in managing the care of these patients[1-4]." inserted page 5 in the chapter ' A rational for surveillance'

- We do not include a methods section explaining the type of review we have performed as the topic is too broad, with so many key search terms from "surveillance and management of Peutz Jeghers or polyposis syndrome, small bowel tumor detection" to all imaging modalities for small-bowel evaluation: MRI, small-bowel follow-through, CT, virtual endoscopy, videocapsule and double balloon endoscopy etc.

- We now present a table summarizing literature data with regards to MRI as it is the emerging modality for surveillance that this paper emphasizes, as we are radiologists, detailing its advantages and limits with regard to other imaging modalities

<u>Specific comments</u>

- We give more details about the occasional malignant appearance of benign polyps, and the very characteristic features which alerts pathologists to the diagnosis, as follows:

"Small polyps in the bowel may display a phenomenon called "pseudo-invasion," which mimics an invasive carcinoma. This pseudo-invasion is an epithelial displacement through the muscularis mucosae

and can be distinguished from a true invasion by the lack of cytological atypia[3,4]."inserted page 4 in the chapter 'Pathological features'.

- We corrected the english mistakes as requested:

"*It is now well acknowledged that polyp size is the most important risk factor for small-bowel intussusception with small-bowel obstruction and that intussusception is generally due to polyps ≥15 mm in diameter[3, 14].*" on page 5.

"*In this regard, Maccioni et al have suggested that a combined MR-enterography technique using two separate image acquisitions, one in supine position and the other in prone position helps increase the number of visible polyps*" on page 6

"*MR imaging using dedicated protocols is now being widely used for the evaluation of the small-bowel in a variety of diseases and has been recently proposed as an accurate technique for the detection of small-bowel tumors[19, 20, 21].*" on page 6.

"*In the study by Gupta et al., polyp visualization was facilitated by striking enhancement, which was more marked in large polyps. However, polyp enhancement is not a function of tumor size alone, as some small polyps also showed significant enhancement and are better detected by gadolinium-enhanced MR sequences (Figure 2)[24].*" on page 7.

"*Among unenhanced MR sequences, balanced MR sequences (e.g.. Fast Imaging with Steady-state in Precession [FISP], balanced fast field echo [FFE], and free induction echo stimulated acquisition [FIESTA]) provide the best conspicuity of polyps.*" on page 7.

- We corrected the legend of the image number 1 it now reads: *macroscopical appearance* instead of *histopathological.*

- We modified the legends of the figures beginning with patient 1, 2 etc.. and replaced "patient "by "polyp".

- Lastly, we now put the images near the relevant text of each figure parts

3 References and typesetting were corrected

Sincerely yours,

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