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US Expert Medical Opinion, Inc. 1625 SE, 3rd Avenue Suite 723. Fort Lauderdale, FL 33316. USA

Date: April 10th, 2020

Reference: Mr.

DOB:

Dear Mr.

The following is a report prepared for Mr. based upon my review of the available medical records provided in your MyUSADr. Medical opinion request.

#1 Office notes from Mr. P dated April 2, 2015.

These records state that Mr. had undergone a 2-stage revIsion left-sided internal hemi-pelvectomy and hip reconstruction. He was 7 months post op. He was having neuropathic pain from a partial sciatic nerve injury. He was walking with a short leg gait because of a 3 cm limb length discrepancy. X-rays at that time state that the implant remains in place with no evidence of loosening or infection. He had nerve conduction studies performed. There is still evidence of a partial lesion of the sciatic nerve, and this is mainly sensory. Mr. Pollack states that laid has full power in dorsiflexion and 4 out of 5 power of ankle plantarflexion. He has pins and needle sensation in the L5 and S1 distributions.

#2 Repeat EMG and nerve conduction studies from March 9, 2016.

This report states that there is a partial left sciatic nerve lesion, axonopathy, affecting peroneal greater than the tibial nerve segments. There are no features of ongoing left lumbosacral radiculopathy. Significant left common peroneal neuropathy at or across the fibular head or knee is less likely.

#3 Office notes from Mr. P dated March 10, 2016.

The records state that Mr. is now 20 months since his 2-stage revision left internal hemipelvectomy and hip reconstruction. It also states that he has undergone gastric band and has lost a significant amount of weight. He walks unaided with a short leg gait as well as a left-sided foot drop. It states that his left leg is approximately 5 cm shorter than the right. He has good active plantar flexion of the foot. He has reduced sensation on the dorsum of the foot. He has no power of ankle and toe dorsiflexion of ankle eversion. The x-rays report states that everything is satisfactory with no signs of loosening. A bone scan shows no evidence of

metastatic disease. The nerve conduction studies confirm a partial left sciatic nerve lesion affecting the peroneal more than the tibial nerve segments. Mr. P recommended a

combination of a foot drop splint and a heel raise.

#4 Medical report from Mr. M, Consultant Orthopedic Surgeon from the peripheral nerve injury unit.

The records state that Mr. is a survivor of pelvic Ewing sarcoma. It states that he had a previous hemipelvectomy and subsequent infection in the prosthetic replacement and excision and further prosthetic replacement in 2014. The hemipelvic replacement operation cleared him of the infection and there was no sign of metastatic disease.

He states that there was aa sciatic nerve lesion affecting his peroneal more than his tibial nerve resulting in a foot drop and pain.

Mr. M felt that Mr. would be an excellent candidate for tibialis posterior tendon transfer.

#5 Report from the orthopedic department from the Kuwait Oil Company ---- Hospital.

This report summarizes that Mr. developed cancer in his left hip bone in 2004. He had been operated upon for a hemipelvectomy and a custom-made prosthesis. This became infected in 2014. In May 2014 he had removal of the prosthesis, traction, and medical management. He underwent another prosthesis surgery in July 2014. He developed immediate postoperative foot drop. He underwent another surgery with shortening. His foot drop did not return back to normal. EMGs performed August 20, 2014 were consistent with sciatic nerve lesion. He had an MRI scan done of the lumbar spine which was normal. EMGs done in October 2016 demonstrated sensory nerve conductions to be normal. The EMG findings were compatible with chronic neurogenic changes involving the peroneal nerve distribution. Examination demonstrated wasting of the calf and thigh muscle and ankle drop. There is ankle plantar flexion but no dorsiflexion. The toes moved freely. There is markedly diminished sensation at the dorsum of the first webspace and the muscles were all weaker compared to the other side.

#6 Letter to the employer from May 23, 2017.

This letter was prepared by Mr. Michael Fox. It states that Mr. underwent multiple tendon transfers about the left foot and ankle. It states that the tendon transfers were required as a consequence of a history of Ewing sarcoma, a hemipelvectomy, and a previous sciatic nerve injury. It states that he recovered well from the initial operation. He was requesting physiotherapy. It states that he will require a period of 6-8 weeks of physiotherapy before he is

able to return to work.

#6 MRI of the left leg from February 11, 2019.

The impression is extensive signal abnormality in the tibialis posterior, flexor digitorum longus, flexor hallucis longus and peroneal muscles as well as in the distal lateral gastrocnemius

muscle. Differential diagnosis includes an inflammatory etiology/denervation edema. Suggest follow-up. There is also a small round area of marrow signal abnormality in the proximal metaphyseal diaphyseal area of the tibia. 2 small to characterize. Follow-up in bone scan suggested.

#7 MRI of the left ankle from February 11, 2019.

The impression is deltoid ligament sprain. Focal marrow edema/contusion in the posterior lateral aspect of the body of the talus. Diffuse edematous signal in the visualized flexor hallucis longus muscle. Pre-Achilles fat pad edema.

#8 Plain x-ray of the left hip from February 11, 2019.

The findings reveal a total hip replacement. Multiple radiopaque shadows are seen lateral aspect of the thigh suggesting calcifications.

#9 CT scan of the left hip from February 11, 2019.

The impression is postoperative changes. Slight widening of the lucency along the bone cement interface in the intertrochanteric region, having a maximum diameter of 2.8 mm. Suggested follow-up to look for interval progression. Bone fusion of the left sacroiliac joint. Few subcutaneous nodular calcific foci in the proximal thigh.

#10 MRI scan of the left foot from February 11, 2019.

Impression is minimal internal or metatarsal bursitis at the third webspace. Otherwise unremarkable study.

#11 Medical report from Mr. P from May 9, 2019.

This report states that Mr. is struggling with several issues including a significant leg length discrepancy with shortening of the left leg as well as weakness in his left foot due to a partial sciatic nerve lesion. He had already undergone tendon transfers which have helped. On exam, there is some active ankle dorsiflexion and plantarflexion. A PET scan was reviewed showing no

evidence of recurrent disease or distant metastasis. A CT scanogram was carried out to measure the leg length discrepancy and he had approximately a 3 cm shortening on the left side from the femur. The report states that Mr. F says there is no more he can do in terms of tendon transfers to improve his ankle function. The question arises as to whether he would be a candidate for lengthening procedure of his femur. He has been referred to DG for evaluation.

#12 Medical report from Mr. P to Mr. D from June 6, 2019

Asking that Mr. be evaluated to see if he is a candidate for a lengthening procedure to equalize

limb lengths.

Impression:

#1 Ewing sarcoma

#2 Status post left hemipelvectomy and left hip reconstruction

#3 Status post infected left hip reconstruction

#4 Status post revision left hip reconstruction

#5 Partial sciatic nerve lesion with an associated foot drop

#6 Status post tendon transfers

#7 Limb length discrepancy of approximately 3 cm

Response to questions from Mr.

Overall I feel that considering his initial diagnosis of a Ewing sarcoma, Mr. has done fairly well. There is no obvious recurrence of the tumor or metastatic disease. The hip reconstruction appears to be doing well. It seems that the tendon transfers helped some but not help completely. I don't feel that any further tendon transfers should be recommended.

From a surgical standpoint, an ankle fusion could be carried out but I think that would be a last resort. I feel that a foot drop brace, AFO, would be a better option at this time because it would still allow plantar flexion.

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With regards to the nerve pain, it is difficult to determine if the pain is coming from the nerve, foot drop, or previous surgeries. Therefore the results of any treatment may not show significant improvement or results. I would therefore recommend continuing medical management and potentially as a last resort to consider a trial of a nerve block and or radiofrequency ablation of the symptomatic nerves.

I feel the biggest question is a limb lengthening procedure. Wearing a 3 cm shoe build up and using an AFO brace is not ideal in light of the foot drop. Limb lengthening procedures are successful, but they do carry potential complications. In light of his previous nerve injury, the biggest concern would be exacerbating his neurogenic pain. However, a limb lengthening procedure is done gradually over time and the risk of further neurogenic pain or injury would hopefully be minimized. I feel that a limb lengthening procedure would give him the best

improvement overall to improve the limb length discrepancy and improve his gait. The limb

lengthening procedure would have to be carried out distal to the cemented femoral stem. It would either have to be done with an external ring system or possibly over a short intramedullary rod. This would depend on the distance between the cemented femoral stem and the remaining diaphyseal portion of the femur.

Thank you for allowing me to assist you with your medical concern. I hope this review supplies the information desired. Please feel free to contact me if you have any further questions

Sincerely,

Bruce Janke, MD

Diplomate American Board of Orthopedics

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US Expert Medical Opinion, Inc. 1625 SE, 3rd Avenue Suite 723. Fort Lauderdale, FL 33316. USA

Date November 16th, 2020

Reference: Mr

DOB:

Dear

The following is a report prepared for Mr. based upon my review of the available medical records provided in your MyUSADr. Medical opinion request.

Source of information: Clinical node (doc), lab (doc)

This is a 58-year-old patient with stage IV lung cancer with liver metastases. The information is obtained from patient brief clinical notes and laboratory data provided on November 10, 2020. In summary, the patient essentially had liver ultrasound which revealed a liver lesion, discussed follow-up by an unenhanced CT scan which showed a liver space-occupying lesion. Again based on the clinical notes provided, the patient had no nausea, vomiting, abdominal pain, bloating. Abdominal examination was unremarkable. The patient blood work performed on October 9, 2020 reveals WBC 5.66 hemoglobin 14.7 platelet count 164. Patient's direct bili was 2.31 mmol/L AST 23.65 ALT 14.60 creatinine 94.31 with no reference ranges provided. Work-up also revealed a positive hepatitis B surface antigen, positive hepatitis B surface antibody. The patient CT scanning on October 17, 2020 revealed an upper left lung nodule; there were also 2 lung nodules scattered in both lungs. MRI revealed nodules in the liver. Biopsy of the lung revealed invasive carcinoma, possibly moderate to poorly differentiated adenocarcinoma TTF-1 positive ALK negative. The patient's final stage was T2N0M1C stage IVb lung adenocarcinoma.

As far as further diagnostic work-up is concerned, I do recommend a PET scan as well as a brain MRI. I also recommend next generation sequencing efforts to identify patients EGFR, ALK, ROS–1, BRAF, MET, HER-2, RET, NTRK status which can potentially be treated with targeted agents.

If the patient does have EGFR or ALK mutations first-line therapy would be osimertinib for EGFR, alectinib for ALK mutations. If the mutational testing is negative for these two mutations chemo-immunotherapy can be considered. Based on NCCN guidelines and current FDA approvals, chemo-immunotherapy options include **carboplatin plus pemetrexed plus pembrolizumab** OR **carboplatin plus paclitaxel plus bevacizumab plus atezolizumab** OR **carboplatin plus paclitaxel plus pembrolizumab** OR **Nivolumab plus ipilimumab plus paclitaxel plus carboplatin**. If the patient is PD-L1 positive first-line Pembrozulumab alone can be also considered. Among all these combinations I personally prefer carboplatin plus paclitaxel

plus Nivolumab plus ipilimumab combination as outlined in Checkmate–9LA clinical trial. The trial demonstrated clinically significant benefit in overall survival in the chemoimmunotherapy group. This regimen consists of paclitaxel 175 mg/m² plus carboplatin AUC 5 for every 3 weeks 2 cycles and Nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks until disease progression or unacceptable toxicity or up to 2 years inpatient without disease progression. Again other options are also very reasonable.

Please note, patient's chemotherapy doses may need to be modified based on the patient's liver and kidney functions or patient's general condition and comorbidities. Patients may have chronic hepatitis B infection. This has to be addressed with a gastroenterologist or infectious diseases specialist ASAP since it may lead to reactivation during chemotherapy.

For ROS1, BRAF, MET, HER-2, RET, NRTK mutations there are treatments available especially in the second or third line setting. For ROS–1 crizotinib, for BRAF trametinib plus dabrafenib, for MET exon 14 capmatinib, for RET selpercatinib, for HER-2 trastuzumab, for NTRK gene fusion larotrectinib can be utilized. Please also note that second line chemotherapy options are also available. If first-line chemoimmunotherapy fails and if the patient has no targeted therapy options chemotherapy docetaxel plus ramucirumab can be considered as a second line option.

There are clinical trial options available for this patient throughout the United States. You may search clinicaltrials.gov for this purpose.

I hope you find this information helpful. Again information is provided based on recent data. Please do not hesitate to contact me if you have any questions.

Sincerely,

Mehmet Hepgur, MD
Diplomate American Board of Internal Medicine, Hematology and Oncology

Reference:

NCCN Guidelines. NSCLC Version 8 .2020

Legal Disclaimer:

The Report is an opinion of a medical expert based on the medical information regarding your case that you provide us. The physician rendering the Medical Report will not have the benefit of examining you in person, the ability to order additional tests, or have any information beyond what you provide. The Report is intended to provide you with information to supplement the information you have already received from your treating physicians. The information contained in the Expert Medical Opinion Report shall not be used to substitute for your physician's recommendations. You should discuss the Report with your own doctors, who are responsible for your care.

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Date: August 23rd, 2020

Reference: Mr.

DOB:

Dear Mr.

Thank you for giving me the opportunity to review your case. You asked for information about the comparative effectiveness of various external beam radiation options in treatment of Prostate Cancer.

The following is a report prepared for Mr. based upon my review of the available medical records provided in your MyUSADr. Medical opinion request.

CC- Mr is a 59 year old male with a palpable T3N0 prostate cancer with Gleason 9 and a PSA 4.3ng/ml

HPI

1. Undergoing routine PSA screening PSA in 2018 of 5.8ng/ml
2. 11/01/2018 Prostate biopsy 12 cores-
   Left base Gleason 3+4 50% only 1 out of 2 cores, PNI
   R apex high grade PIN
3. 2/27/2019 MRI prostate without gad with ADC multiparametric, with small field of view, with dynamic enhancement- L peripheral zone lesion at the interface of base and mid gland- no frank ECE, apical peripheral zone Pirads 4
4. Offered EBRT vs brachytherapy- no treatment performed
5. 3/12/2020 MRI prostate- with ADC multiparametric, with small field of view, with dynamic enhancement-
   With comparison to a 2/25/2019 scan- shows a left peripheral zone with early extracapsular extension, and possible seminal vesicle involvement
6. 6/11/2020 US guided biopsy of the prostate with MRI fusion of L new peripheral zone lesion Prostate gland volume at 28cc
   PSAD 0.16
   PSA 4.3 ng/ml

7. 6/11/2020 Pathology Gleason 4+5, 5/5 cores involved with max core involvement of 60%, with invasion of extraprostatic fat
8. Currently planned for ADT (androgen deprivation therapy and radiation treatment

AUA score 2
SHIM 24
No GI complaints

PMH

1. Herniated disc
2. Polyps on colonoscopy- 2.5 years
3. No hx of IBD

FMH

1. Father died of pancreatic ca
2. Mother died of bladder cancer

Social History

ETOH-10 beers a week
Married lives with his wife
Exercise- Cardiovascular 4 times a week and weight lifts 3x a week

Medications

1. Vitamin B12
2. Probiotics
3. Vitamin D and K
4. B complex
5. Pygeum

PSA Results

5/28/14- 1.0
7/28/15- 1.3
11/19/15- 1.6

3/10/2016- 1.5
2/14/2017- 2.4
7/10/2017- 3.0
3/16/2018- 3.6
10/5/2018- 5.8
12/31/2018- 5.8
4/19/2019 -5.4

8/19/2019 -5,3
12/5/2019- 4.4

Assessment

Mr is a 59 year old male with a palpable T3N0 prostate cancer with Gleason 9 and a PSA 4.3ng/ml
NCCN guidelines would consider this a h**igh risk localized prostate cancer-** considering the Gleason 9 and T3/ExtraCapsular involvement
Life expectancy- 23.7 years

Plan

1. Treatment options
    a. External beam radiation (EBRT) (7-9 weeks of radiation)and Androgen Deprivation Therapy (ADT) for 1.5 years- 3 years
    b. External beam radiation (5 weeks) plus brachytherapy plus ADT for 1-3 years
    c. Surgical excision plus lymph node dissection- which will likely be followed by radiation and likely ADT

Recommendations-
The combination of EBRT plus brachytherapy plus ADT represents a more aggressive treatment option and has been shown to provide a better biochemical control (i.e. PSA control) compared to EBRT + ADT without brachytherapy. This has become the standard of care according to some guidelines.

(https://pdfs.semanticscholar.org/3cd0/e10e13f57695c8c0b9e5f1d95931884e7a4f.pdf)
However an increase in risk of long term toxicity with this brachytherapy boost has been noted.(https://www.redjournal.org/article/S0360-3016(17)30008-1/fulltext) and no survival benefit has been shown. (https://ascopubs.org/doi/10.1200/JCO.2018.78.6236)
A less aggressive approach with equal survival outcomes would be EBRT with 2-3 years of ADT. This has equivalent survival benefit and lower risk of long term GI and GU side effects

This patient has excellent pretreatment urinating function and with most likely tolerated both options well. It is important that the provider who performs the brachytherapy has a vast and current experience with this technique

2. Radiation treatment techniques
    a. Protons- This technology will lower the total dose of radiation to the surrounding tissues. There remains significant debate if there is benefit to protons for prostate cancer over IMRT. Current evidence has not shown a significant benefit and the outcomes appear the same. https://pdfs.semanticscholar.org/3cd0/e10e13f57695c8c0b9e5f1d95931884e7a4f.pdf- This resource is not widely available, and I would not recommend traveling for it. In addition in this patient case the possible benefit of protons seems limited as the amount of radiation from the external component is reduced as the patient is planned for brachytherapy.
    b. IMRT- Intensity Modulated Radiation is a well established technique which has been shown to reduce toxicity in patients receiving radiation over the older 3D conformal technique. https://pubmed.ncbi.nlm.nih.gov/24113055/. In addition strong consideration should be given to radiation of the patient pelvic lymph nodes (see below). In that setting IMRT will likely lead to lower dose to the small bowel. https://pubmed.ncbi.nlm.nih.gov/11020560/.
    c. SBRT- Stereotactic body radiation- is using 5 fractions of high dose of radiation to the prostate. This is a promising technique which is very convenient for patients. However, this treatment as a standalone treatment would not be appropriate for this patient and his high risk prostate cancer. Some centers are using SBRT in combination with IMRT, but the data is very preliminary. I would not recommend this option.

3. IGRT- image guided radiation- allows for daily localization of the radiation treatment and improves accuracy as the prostate gland, bladder and rectal filling can vary daily. Multiple solutions are available to help with prostate targeting including on board CT scan, fiducial markers and Ultrasounds. Evidence points to a reduction in toxicity and improved outcomes with IGRT. https://pubmed.ncbi.nlm.nih.gov/30071296/

4. Pelvis Lymph nodes- some controversy exists about the need to give radiation to the pelvis lymph node in the setting of no pathologic nodes on MRI scan. No randomized study has shown a benefit of whole pelvis lymph nodes. https://pubmed.ncbi.nlm.nih.gov/17531401/. However in patients with gleason 9 cancer there is likely >15% chance of pelvis lymph node involvement as such it is reasonable to recommend treatment to the lymph nodes.

5. ADT- androgen deprivation therapy
    a. This treatment works by lowering the testosterone level of the patient, as the cancer is fueled by the testosterone. It has been well established to be an effective agent in improving overall survival in patients with high risk prostate cancer over Gleason 8. This is strongly recommended in this patient case.
    b. Length of therapy- There remains controversy about the length of ADT most guideline advocates for 2-3 years. However, if patients are tolerating the ADT poorly then as short as 18 months could be used. https://ascopubs.org/doi/10.1200/JCO.18.00606?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
    c. Mitigation steps- ADT is associated with multiple side effects including loss of libido, loss of muscle mass, hot flashes, breast tenderness, fatigue, cardiovascular events, diabetes and possible memory loss (less of a concern in this patient)
        i. Patients need to be encouraged to take daily calcium 1000mg-1200mg and Vitamin D 400-1000 IU.
        ii. FRAX score- will likely be very low (I dont have the patient high or weigh) If it is elevated would recommend a dexa study.
        iii. Resistance training (2 a week) in addition to cardiovascular training (150 minutes of moderate work) should be be encouraged to decrease the risk of muscles loss

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Thank you Mr. for allowing me to review your records and assist you with your medical condition. Best wishes for a quick recovery. Please feel free to contact me at any time to discuss my review and/ or the results of the recommended workup.

Sincerely,

Evan Landau, MD

Diplomate American Board of Radiation Oncology