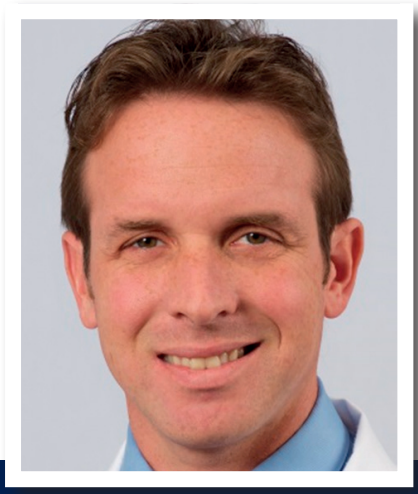
A CASE OF METASTASIZED RENAL CELL CARCINOMA



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- **February 2002:** excision of a dermal lesion, infracapsular on the left side Histology (pathology lab Länggasse Bo2.0534ß): Subcutaneous metastasis (diameter 1.2 cm) of a clear cell renal cell carcinoma (RCC), R0 resection
- **February 2002:** CT thorax-abdomen-pelvis: No enlarged lymph nodes, postoperative changes in thyroid bed. Status after nephrectomy. No lung or liver metastases
- **Follow-up at that time:** active surveillance

Diagnosis: Metastatic RCC in a 75 year old patient

The advent of targeted therapy has dramatically changed the therapy of metastatic RCC during the last decade. In this case report, we will discuss the possibilites of targeted therapy in an elderly patient with relapsed RCC.

Mr. H. Z., born in 1941 – Case history

- **1995:** first diagnosis of a renal cell carcinoma (RCC) on the left side
- **Left tumour nephrectomy. Histology:** clear cell RCC 7.0 x 5.5 x 5.5 cm with infiltration of the renal capsule
- **Tumor stage:** pT2 pN0 cM0 G2
- **Follow-up at that time:** wait and see
- **September 2001:** MRT upper thoracic aperture: left thyroid nodule 3 cm, activated sternoclavicular osteoarthritis
- **February 2002:** left total thyroidectomy, right subtotal thyroidectomy
- **Histology (pathology lab Länggasse Bo2.04144):** Left: total thyroidectomy specimen with two metastases of a clear cell RCC (diameter 1.6 cm and 2.4 cm), distinct signs of angioinvasion, R0 resection. Right: subtotal hemithyroidectomy. Specimen with broken nodule of a RCC metastasis (diameter 1.5 cm), wide margins, R1 resection

What follow up is appropriate?

75% of the participants advocated active surveillance with regular imaging. Another 25% supported adjuvant therapy with a tyrosin kinase inhibitor (TKI) ***(figure 1).***

The third selection is the correct answer.

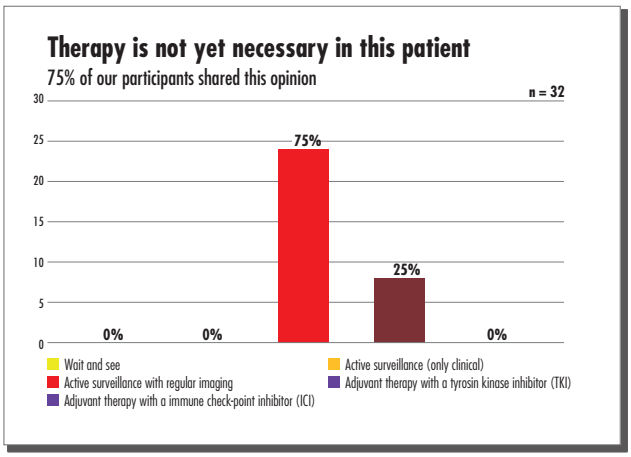


Figure 1
Question 1 of the case report: «What follow-up would have been appropriate in 2016»

RCC is recognised as having a very variable natural history. In the current ESMO guidelines, laparoscopic radical nephrectomy is the preferred option in T2 tumours (> 7 cm). However, there is no recommended adjuvant therapy.[1] Therefore, active surveillance with regular imaging is the right approach at this stage.

To date, no effective adjuvant treatment for renal cell carcinoma (RCC) has been described, but research in this area is important since the 5-year relapse rate for intermediate- and high-risk early-stage RCC is 30%–40%.[2] In addition to surgical management, relapse risk reduction through adjuvant therapy is thus a very important goal in these patients. Adjuvant therapy with the TKI sunitinib showed conflicting results: in the phase 3 trial (ASSURE) involving patients with locally advanced renal-cell carcinoma, investigators did not find any treatment advantage for adjuvant therapy with sunitinib or sorafenib over placebo.[3] However, a trial published only a month ago showed that patients with locoregional renal-cell carcinoma at high risk for tumour recurrence after nephrectomy who were receiving adjuvant treatment with sunitinib had a longer duration of disease-free survival than did those receiving placebo.[4] Median duration of disease-free survival was 6.8 years in the sunitinib group versus 5.6 years in the placebo group (p = 0.03). The safety profile in patients treated with adjuvant sunitinib revealed moderate declines in quality of life while receiving active treatment

Consensus guidelines recommend consideration of clinical trial enrollment to deliver potential adjuvant treatment to patients with intermediate or high relapse risk from early-stage RCC.[1] The results of seven large, multicenter, placebo-controlled, double-blind, randomized adjuvant trials investigating the potential benefit of targeted anti-angiogenesis therapies are expected over the coming years and will shed more light on this important issue in the future.[2]

Further course of disease

2005: Second relapse: In a follow-up imaging in 2005, a soft tissue metastasis ***(figure 2),*** a metastasis in the thyroid bed ***(figure 3)*** and metastases in the pancreas ***(figure 4a and 4b)*** are detected.

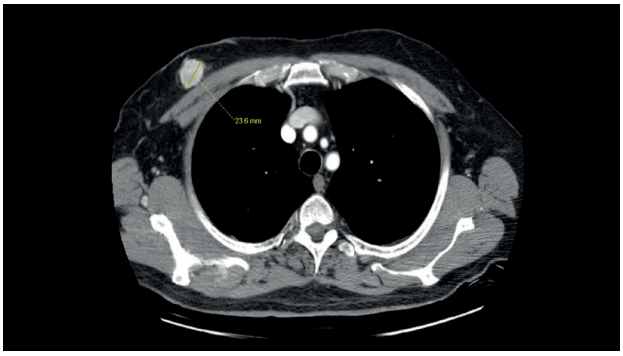


Figure 2: Soft tissue metastasis

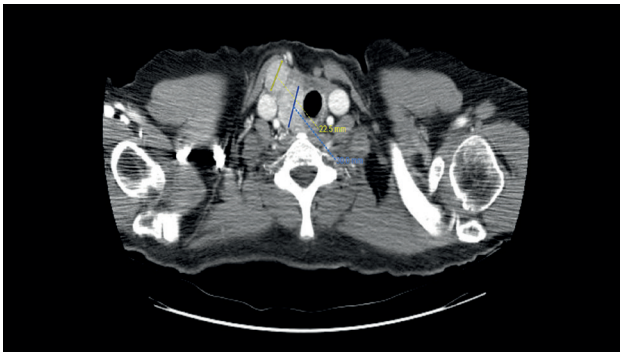


Figure 3: Metastases in the thyroid bed

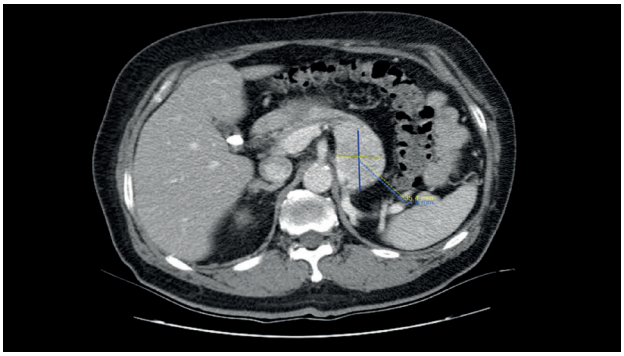


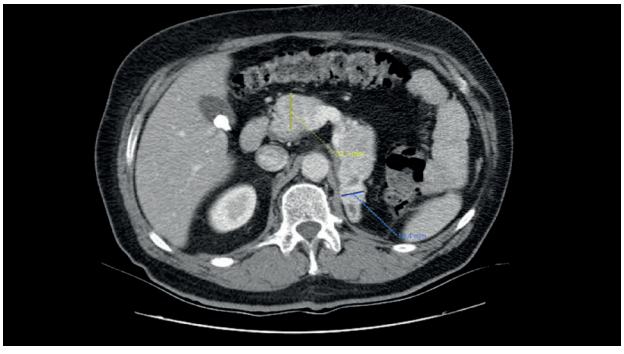
Figure 4a and 4b: Pancreatic metastases

Further course of disease

- **September 2005:** extended total thyreoidectomy of the remaining tissue right including resection of the M. sternocleidomastoideus, M. omohyoideus, M. sternothyreoidius and sternohyoideus as well as lymphnode metastases in the cervicocentral compartment. Excision of a skin lesion infracapsular on the left side

- **November 2005:** subtotal pancreas resection with splenectomy, pylorus-preserving pancreaticoduodenectomy as well as cholecystectomy

- **January 2008:** CT abdomen-pelvis: small round lesion (known for long)



4b

left latero-basal corresponding to a granuloma. In addition, no other tumour detection

- **2009:** third relapse: In a follow-up imaging in 2009, a bone erosion at the shoulder blade ***(figure 5)*** and a soft tissue metastasis ***(figure 6)*** are detected.

How to proceed after the third relapse?

75% of the participants recommended systemic therapy with a tyrosine kinase inhibitor (TKI), another 50% preferred radiation, further 25% wanted to give only analgetic medication and 25% voted for a surgical procedure ***(figure 7).***

The right answers are systemic therapy with TKI and radiation.

Treatment of metastatic renal cell carcinoma (mRCC) has changed dramatically in the last 10 years, mainly due to the advent of targeted therapy (TT). Antiangiogenic therapies, including the vascular endothelial growth factor (VEGF) pathway inhibitors sunitinib and sorafenib showed to be effective in patients with mRCC.[5] In an analysis of the mRCC database, outcomes of mRCC patients treated with 1, 2 or 3+ lines of TT were compared.[6] 57% of patients only received first-line TCC, although patients who were able to receive more lines of TT lived longer. Therefore, it is of critical relevance, to treat patients as effective and as long as possible. In the ESMO guidelines, sunitinib is recommended as first-line treatment in mRCC for patients with good to intermediate prognosis.[1] In a phase III randomized clinical trial, sunitinib more than doubled progression free survival (PFS) compared to IFN-α (11 months vs. 5 months; $p < 0.001$) in patients with mRCC and no prior treatment with systemic therapy. Sunitinib was also associated with a higher objective response rate than was IFN-α (31% vs. 6%; $p < 0.001$). Patients also reported a significant better quality of life with sunitinib compared to IFN-α ($p < 0.001$).[7] Long term follow up of this trial showed a strong trend toward improved OS vs. IFN-α in the first line setting (26.4 vs. 21.8 months, $P = 0.051$).[8] Therefore, sunitinib remains a commonly used first-line agent, which is also superior to the TKI sorafenib that only showed non-inferiority compared to IFN-α.[5] Response rates increase over time: At the follow-up assessment after 11 months, response rate was 47%.[8]

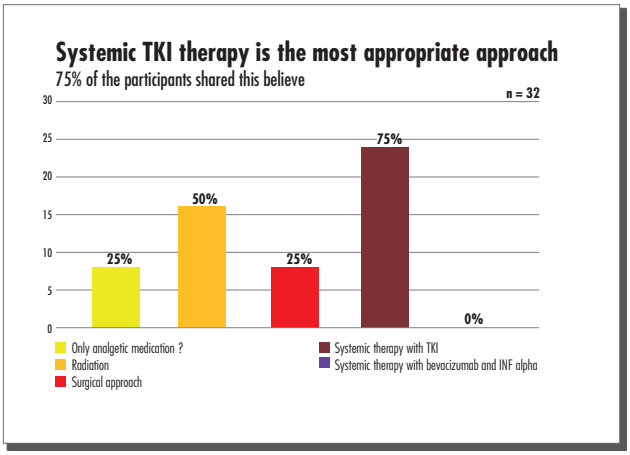


Figure 7
Question 2 of the case report: «What treatment of this third relapse would you suggest in the TKI era (2009)?» (*multiple choices eligible)*

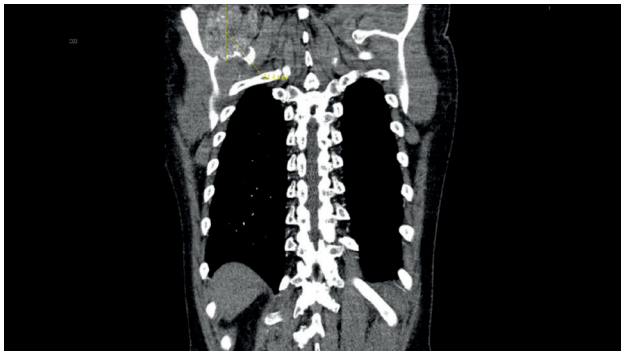


Figure 5: Bone erosion of the spina scapulae on the right side

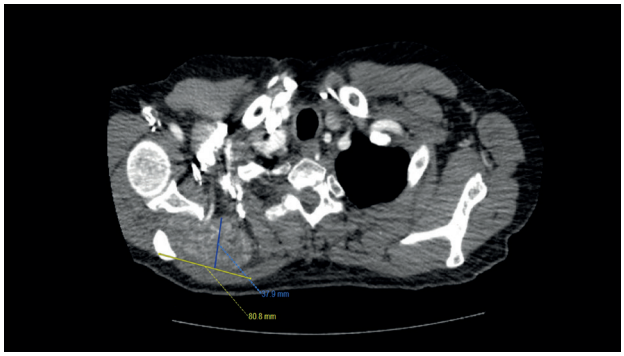


Figure 6: Soft tissue metastasis

A couple of trials assessed how to sequence targeted therapies for mRCC to maximise clinical benefit: In the phase II trial RECORD-3, first-line everolimus followed by sunitinib at progression was compared with the standard sequence of first-line sunitinib followed by everolimus in patients with metastatic renal cell carcinoma.[9] The primary objective was to assess progression-free survival (PFS) noninferiority of first-line everolimus compared with first-line sunitinib. As everolimus did not demonstrate noninferiority compared with sunitinib as a first-line therapy, the trial results support the standard treatment paradigm of first-line sunitinib. The SWITCH trial evaluated sequential use of sorafenib followed by sunitinib versus sunitinib followed by sorafenib.[10] In this trial, both drugs provided overall clinical benefit, regardless of treatment sequence. These data confirm the role of sunitinib in fist-line treatment of mRCC.

Radiotherapy has a limited role in the primary management of renal cancer. However, according to the ESMO guidelines, radiotherapy can be used to treat symptomatic bone metastasis.[1] In this case, local radiotherapy either as a single fraction or fractionated course can provide symptom relief in up to two-third of cases with complete symptomatic responses in up to 20%–25% -I, A recommendation].[1] Therefore, this answer is also correct.

Further course of disease

- **March 2009:** Tumourboard Spital Liestal: Suggestion of a chemotherapy with the TKI sunitinib (three cycles) followed by percutaneous radiation therapy with thermosensitizing. Subsequently presentation in the orthopaedic consultation

- **December 2009:** After three cycles with sunitinib as well as radiation with hyperthermia a CT of thorax-abdomen-pelvis shows: regression of the metastatic mass around the right scapula from 86 x 33 mm to 65 x 39 mm. In addition, no lesions suspicious of metastases. Tumor mass 133.2 cm^3

- **February 2010:** orthopaedic evaluation: conservative therapy is recommended, as R0 resection is only possible with major functional damage.

What to do with the remaining tumour?

Half of the participants voted for active surveillance. Another 50% would rather resume therapy with sunitinib ***(figure 8).***

The right answer is active surveillance.

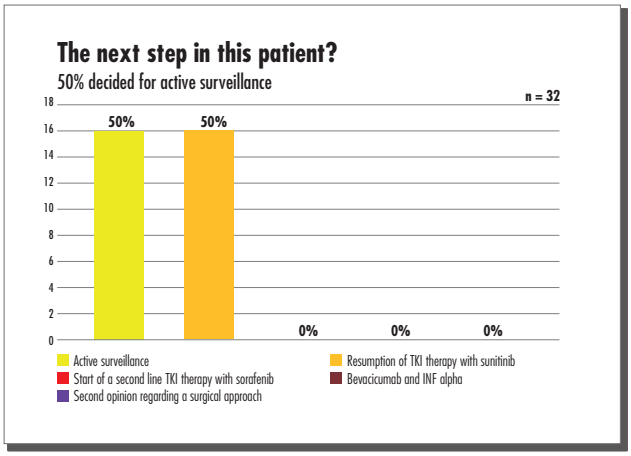


Figure 8
Question 3 of the case report: «How should the remaining big tumour be treated?»

As a resection is only possible with major functional damage, active surveillance Is the only possibility left in our patient.

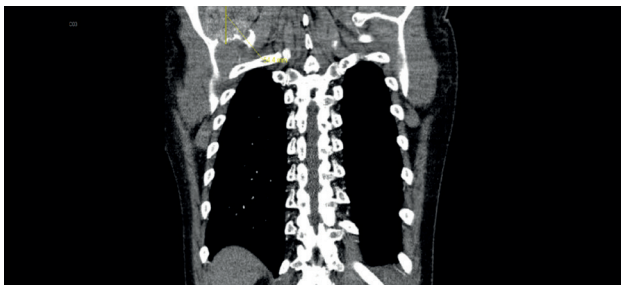


Figure 9: Bone erosion of spina scapulae on the right side

In general, active surveillance is a valid option in patients with mRCC, a disease that sometimes presents with an indolent course without any significant symptoms. In a retrospective trial in 58 mRCC patients who were followed up with deferred treatment for the purpose of active surveillance between 2000 and 2012, 83% hat stable disease and 17% progressive diseases.[11] With a median follow-up of 31,4 months, the median time to progression was 12.4 months (95 % confidence interval 8.4-16.5). A metaanalysis including 5 trials confirmed that patients with asymptomatic, low-volume metastatic disease may benefit from a period of observation free from the toxicity of systemic therapy without compromising survival.[12]

Otherwise, metasectomy can be considered and performed after multidisciplinary multidisciplinary review for selected patients with solitary or easily accessible pulmonary metastases, solitary resectable intra-abdominal metastases, a long disease-free interval after nephrectomy, or a partial response in metastases to immunotherapy or targeted therapy.[1] However, according to the orthopaedic evaluation, this was not possible without major functional impairments in our patient.

Further course of disease

- **March 2010:** CT thorax: Further discrete regression of metastasis close to M. supraspinatus 7.0 x 4.2 x 3.7 cm, tumour mass 108.8 cm^3

- **April 2010–June 2015:** active surveillance without relevant changes of local findings. In the meantime, small nodules in the lung (mmm range/no change in size) were demonstrated in the follow-up imaging

- **July 2015:** CT thorax-abdomen-pelvis: Compared to the previous assessment in December 2014 significant increase of bone destruction as well as the whole tumour mass from 4.5 x 6.5 x 4.5 cm to 8.2 x 7.4 x 6.6 cm. No new osteolysis in other parts of the skeleton, no further metastases

- **2015:** fourth relapse: In a follow-up imaging in 2015, bone erosion of the spina scapulae ***(figure 9)*** and a soft tissue metastasis ***(figure 10)*** are detected

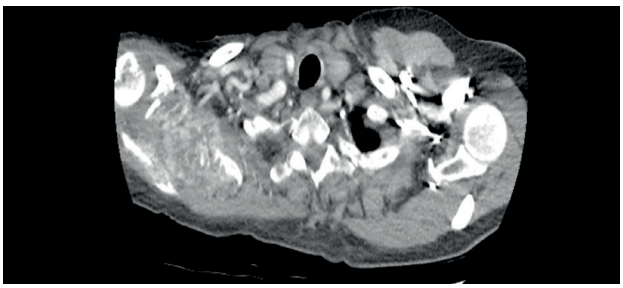


Figure 10: Soft tissue metastasis

What treatment can you offer to the patient?

A TOR-inhibitor was a right choice for 50% of voters. 25% opted for a second TKI, another 25% for palliative analgetic re-radiation ***(figure 11).***

The right answers are 3 and 5.

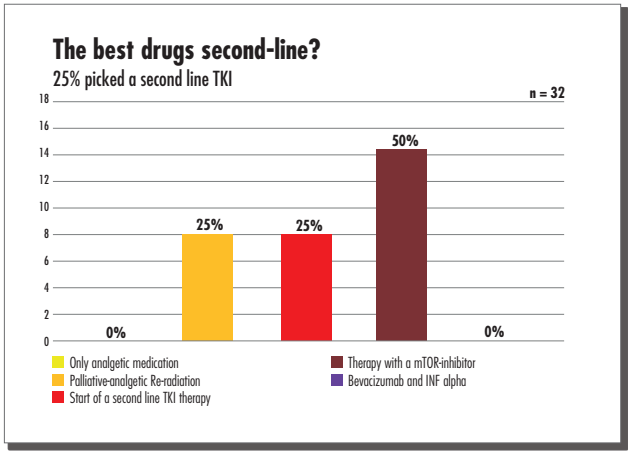


Figure 11
Question 4 of the case report: «How to deal with this new locoregional progression?»

Treatment sequencing in second-line after first-line TKI failure may consist of either a second-line TKI or a second-line mammalian target of rapamycin (mTOR) inhibitor.[13] However, the latter is rarely used after the approval of nivolumab.

In a retrospective cohort trial was shown that median OS in patients who received only one line of therapy was 14.9 months from the time of first-line therapy initiation (95% CI, 13.2–16.7 months), with PFS of 6.7 months (95% CI, 5.9–7.5 months). In contrast, the median OS in patients who received two lines of therapy was 21.0 months, measured from the time of first-line therapy initiation (95% CI, 19,1–23.5 months), with PFS of 3.4 months, measured from the time of second-line therapy initiation (95% CI, 3.0–3.9 months).[6] Although this study is limited by its retrospective design, patients benefit from early and long effective treatment.

We started second line therapy with pazopanib. This agent has shown activity in patients with mRCC and 2 prior lines of therapy, including at least one vascular endothelial growth factor directed therapy.[14] Axitinib would have been another possible option for our patient. In the ESMO guidelines, axitinib and everolimus are recommended for secondline treatment after first-line treatment with VEGFtargeted therapy.[1]

The recommendation of the TOR-inhibitor Everolimus is based on a phase III trial, which included metastatic renal cell carcinoma patients whose disease had progressed on VEGF therapy. In this trial, everolimus significantly prolong progression-free survival compared to placebo.[15] In the AXIS trial, axitinib, a potent and selective second-generation inhibitor of VEGF receptors was compared with sorafenib as secondline therapy.[16] Included patients had progressed despite first-line therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib ($p < 0.0001$). However, in both trials these agents failed to improve overall survival.[1]

Further course of disease

- **July 2015:** start of a palliative TKI therapy with pazopanib. Another radiatio due to predisposition not possible (elevated risk in the area of plexus-/brachialis)
- **December 2015:** CT thorax-abdomen-pelvis: increasing size of the hypervascularisated metastasis ***(figure 12)*** around the scapula on the right side, 9.1 x 6.9 cm versus 8.5 x 5.9 cm

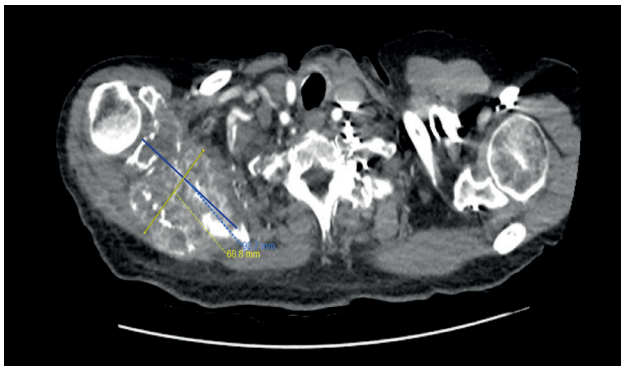


Figure 12
Question 4 of the case report: «How to deal with this new locoregional progression?»

What is most beneficial for this patient?

75% of participants would have given a TOR-inhibitor. 25% voted for a local intervention ***(figure 13).***

The right answer is local intervention to avoid fracture of the scapula.

Transarterial embolization procedures are loco-regional therapies for the treatment of primary and metastatic malignancies. Bland embolization refers to the infusion of embolic materials via the nutrient artery in order to cause occlusion of the tumor arterioles.[17] Embolisation of distant metastases of mRCC for relief of

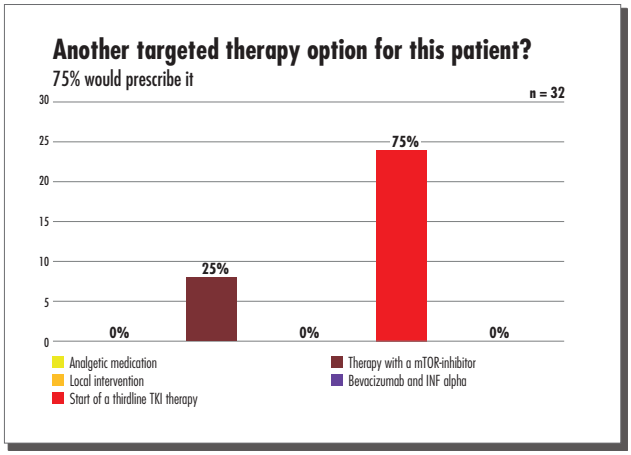


Figure 13
Question 5 of the case report: «What further treatment is necessary considering the repeated locoregional progression during therapy with pazopanib?» (*multiple choices eligible*)

pain has been successful for lesions in different regions such as the vertebral column, limbs and pelvis.[18] As the patient progressed already on 2 TKIs, he will probably not benefit from another systemic therapy.

Further course of disease

- **December 2015:** embolisation of a tumour vessel in the shoulder of the right side ***(figure 14).*** Continuous therapy with pazopanib
- **February 2016 CT thorax:** Positive tumour response with reduction of maximum tumour spread by –25% ***(figure 15)***

Further course of disease

- **May 2016:** CT Abdomen-thorax-pelvis: Unchanged state of the right scapula with tumour infiltration. Loosened bone structure in the area of T1 and C7 indicating a progressive, osseous metastasis. No additional findings
- **May 2016:** start of an antiresorptive therapy with denosumab
- **July 2016:** change of systemic therapy from pazopanib to nivolumab in the course of the early access program
- **At present:** good general condition, nivolumab is tolerated without problems, further imaging planned latest in the end of 2016

Thank you very much for your participation. You will be cordially invited to view the results and conclusions of this survey, which will be summarized and explained by Dr. med. Philippe von Burg. You will receive the link to the analysis by e-mail at a later stage.

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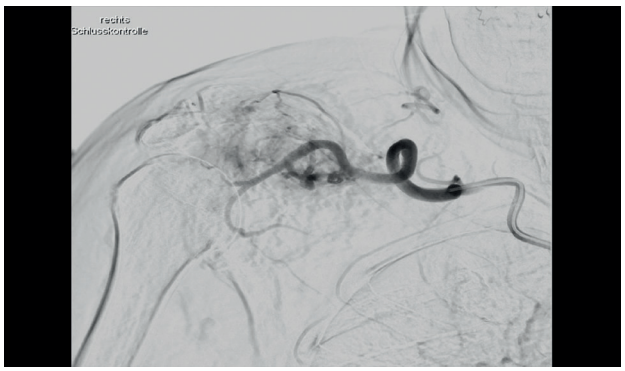

Figure 14: Bone erosion of spina scapulae on the right side

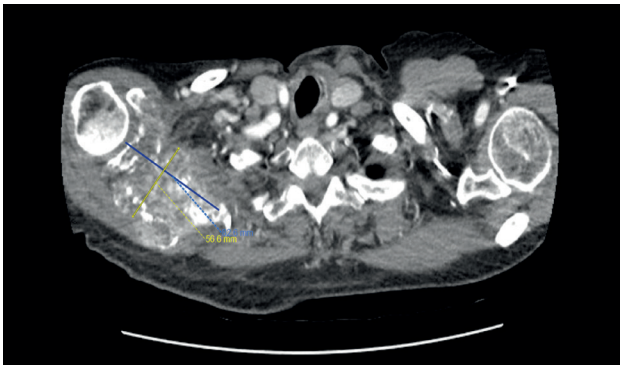

Figure 15: Bone erosion of spina scapulae on the right side

Key-Message 1:

Targeted therapy has revolutionized treatment options in mRCC

- The VEGF-inhibiting agents Bevacizumab, Sunitinib and Pazopanib are recommended for the first-line therapy of patients with mRCC and good or intermediate prognosis ***(figure 16)***[1]
- All three drugs have improved PFS over either Interferon-α or placebo[1]
- Sunitinib improved PFS ***(figure 1)*** and showed a strong trend for better OS[7,8]
- Less fatigue and better quality of life were another advantages of this therapy [7]
- After first-line treatment with VEGF-targeted therapy, both the TKI axitinib and everolimus are recommended second-line due to their improvement of PFS but not OS.[1]

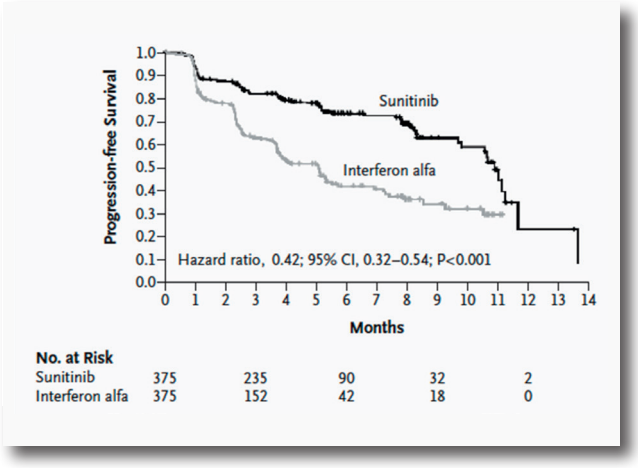

Figure 16: Sunitinib significantly improved PFS compared to Interferon-α.[7]

References

1. Escudier B, Porta C, Schmidinger M *et al.* Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 (Suppl 7): vii65-vii71.
2. Janowitz T, Welsh S, Zaki K *et al.* Adjuvant therapy in renal cell carcinoma – past, present and future. Semin Oncol 2013;40:482-91.
3. Haas NB, Manola J, Uzzo RG, *et al.* Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008-2016.
4. Ravaud A, Motzer RJ, Pandha HS *et al.* Adjuvant sunitinib in high-risk rena-cell cacinoma after nephrectomy. New Engl J Med 2016, October 10, 2016. DOI: 10.1056/NEJMoa1611406.
5. Thomas JS, Kabbinavar F. Metastatic clear cell renal cell carcinoma: a review of current therapies and novel immunotherapies. Crit Rev Oncol Hematol 2015;96:527-33.
6. Ko JJ, Choueiri TK, Rini BI *et al.* First-, second-, third-line therapy for mRCC: benchmarks for trial design from the IMDC. Br J Cancer 2014;110:1917.22,
7. Motzer RJ, Hutson TE, Tomczak P *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
8. Motzer RJ, Hutson TE, Tomczak P *et al.* Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–90.
9. Motzer RJ, Barrios CH, Kim TM *et al.* Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2014;32:2765-72.
10. Eichelberg C, Vervenne WL, De Santis M *et al.* SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. Eur Urology 2015; 68:837-47.
11. Park I, Lee JL, Ahn JH *et al.* Active surveillance for metastatic or recurrent renal cell carcinoma. J Cancer Res Clin Oncol 2014;140:1421-8.
12. Pickering LM, Mahgoub MO, Mukherji D. Is observation a valid strategy in metastatic renal cell carcinoma? Curr Opin Urol 2015;25:390-4.
13. Sun M, Larcher A, Karakiewicz PI. Optimal first-line and second-line treatments for metastatic renal cell carcinoma: current evidence. Int J Nephrol Renovasc Dis 2014;7:401-7.
14. Pal SK, Hossain DM, Zhan Q *et al.* Pazopanib as third line therapy for metastatic renal cell carcinoma: clinical efficacy and temporal analysis of cytokine profile. J Urol 2015;193:114-21.
15. Motzer RJ, Escudier B, Oudard S *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449–456.
16. Rini BI, Escudier B, Tomczak P *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011; 378: 1931–1939.
17. Hickey R, Vouche M, Sze D *et al.* Cancer Concepts and Principles: Primer for the Interventional Oncologist-Part II. J Vasc Interv Radiol 2013;24:1167-88.
18. Goode JA, Matson MB. Embolisation of cancer: what is the evidence? Cancer Imaging 2004;4:133-41.

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