# You're the Flight Surgeon: Renal Cell Carcinoma

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You are the flight surgeon at a small military medical facility, where you are performing your first flight physical examination after recently completing your flight medicine training. Your patient is a 34-yr-old pilot of a single-seat aircraft who presents to the flight medicine clinic for his annual flight physical. He is in his usual state of health and denies any pertinent medical history. Last year he underwent a left inguinal hernia repair, left varicocelectomy, and vasectomy without complication. Surgical history is also notable for circumcision as a newborn. He performs testicular self-examinations and denies any changes in his testicles or scrotal area. He takes no medications, denies use of supplements, and has no known drug allergies. His immunizations are up to date. His annual hearing and vision screenings are normal. He has no fitness or duty restrictions. He is married and has four healthy children, ages 2, 4, 6, and 7 yr old. He denies any alcohol consumption or history of tobacco use. His family history is significant for the following: father—hypercholesterolemia; mother—hypertension, skin cancer; maternal grandmother—colon cancer; paternal grandfather—cardiovascular disease.

On physical examination, his vital signs are within normal limits, including a blood pressure of 124/78. Body mass index is 28.19 $kg \cdot m^{-2}$. As you auscultate his lungs, he asks you to check his "jalapeño hump" in a humorous and off-handed manner. Your remove your stethoscope from your ears with a quizzical expression, not certain if you heard him accurately. He repeats his question at your request and further explains that whenever he eats foods that cause excessive gas production, he feels a firmness in his left upper abdominal area. Visual inspection of the abdomen reveals no distention or peristalsis. Bowel sounds are present in all four quadrants without diminishment. A large, nontender, intra-abdominal mass is palpated in the left upper quadrant, with an irregular inferior border that extends more than 12 cm below the left costal margin in the midclavicular line. The same area is dull to percussion. There is no costovertebral angle tenderness or flank tenderness. Genitourinary exam reveals no scrotal varices, masses, or hernias.

**1. What are some causes of a painless abdominal mass in an adult male?**

A. Organ enlargement: splenomegaly, hepatomegaly, hydronephrosis.
B. Cancer: colon, stomach, liver, pancreas, kidney.
C. Pancreatic pseudocyst.
D. Abdominal aortic aneurysm.
E. All the above.

**ANSWER/DISCUSSION**

**1. E.** The differential diagnosis of an abdominal mass is extensive and includes all the above, as well as constipation, bowel obstruction, leukemia, lymphomas, and primary or metastatic malignancy, in addition to other, less common etiologies. Given the broadness of the differential diagnosis, obtaining a detailed history and performing a thorough physical examination are vital. Factors that help to narrow the differential include the age and gender of the patient, location and size of the mass, character on palpation (e.g., tender or nontender, firm or soft, nodular or smooth, with well-defined or irregular borders, presence or absence of pulsations), other presenting signs or symptoms (e.g., sequelae of liver failure, urinary symptoms, bowel symptoms, etc.).[9] Social and family histories also help to guide further diagnostic evaluation (e.g., history of excessive alcohol consumption, smoking history, family history of malignancy). While it is unlikely that a definitive diagnosis will be established without additional testing, the choice of which diagnostic studies to pursue can be facilitated by forming a broad differential and narrowing the possibilities through a focused but complete history and physical examination.[1,9]

**2. To assess for the more worrisome conditions possibly causing a painless abdominal mass in this young, otherwise healthy man, what is your diagnostic test/study of choice?**

A. Abdominal computed tomography (CT) scan.
B. Abdominal ultrasound (US).
C. Abdominal X-ray.
D. Abdominal magnetic resonance imaging (MRI).
E. Esophagogastroduodenoscopy.

**ANSWER/DISCUSSION**

**2. A.** Noninvasive techniques used to initially evaluate abdominal mass include X-ray, ultrasound, CT, or MRI. There are advantages and

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disadvantages of each, and the use of a particular study depends on the organ being investigated and the availability of the test.[12] Both US and CT are exceptional for confirming or excluding the presence of a palpable abdominal mass and will typically demonstrate the involved organ(s) and/or structures.[6,13] If available, US is a safe, inexpensive, and noninvasive option with the benefit of avoiding exposure to nonionizing radiation.[12] It is often the primary modality used to assist in the identification of intra-abdominal masses, especially in radiation-sensitive populations (e.g., pregnant or pediatric patients).[5,6,12] However, ultrasonography is more operator dependent than other imaging techniques and the visualization of lesions can be hampered by physique or the presence of superimposed bowel gas.[5,12] Given the elevated risk of malignancy, the National Comprehensive Cancer Network (NCCN) recommends use of contrast-enhanced, multidetector CT as the first-line imaging modality.[13] The benefit of CT imaging is that it can simultaneously characterize the mass and provide information about the presence or absence of metastasis.[13] On the other hand, CT imaging is more costly than US and involves ionizing radiation.[12] MRI provides diagnostic images of similar usefulness to CT and US while offering several advantages.[5] It is excellent for characterization of tissue composition (e.g., protein, fluid, fat, and vascular components) and does not involve exposure to ionizing radiation.[5] Nonetheless, MRI is relatively expensive, may not be easily accessible, and may be contraindicated in individuals with claustrophobia or implanted metallic medical devices.[12] Plain radiography is least expensive and is more readily attainable compared to other imaging modalities, but it also offers the least diagnostic information.[1] While obtaining a plain radiograph as an initial test is not an inappropriate approach, it is unlikely to indicate a diagnosis and may delay more definitive testing while also exposing the patient to radiation.[5] Esophagogastroduodenoscopy can be used to identify intraluminal gastrointestinal (GI) masses. It offers the ability to perform a tissue biopsy while simultaneously providing visual characterization of the mass. However, it is not the appropriate initial diagnostic test of choice for most patients given its inability to evaluate for extraluminal or non-GI disease.[13,15]

You obtain additional history. The patient reports that the first noticeable symptom was abdominal firmness, which began approximately 1 yr ago. He denies fevers, chills, fatigue, recent weight changes, nocturnal sweats, recurrent infections, abdominal pain or distention, postprandial fullness or early satiety, excessive eructation or flatulence, nausea, vomiting, diarrhea, constipation, change in stool pattern or color, steatorrhea, back or bone pain, hematuria, problems with urinary frequency or urgency, jaundice, dyspnea, extremity edema, myalgia, or muscle stiffness. He denies any personal history of malignancy and provides this additional family history: mother—basal cell carcinoma; sister—melanoma; paternal grandmother—kidney cancer.

A radiograph of the kidneys, ureters, and bladder reveals a large mass with a diameter of 17 cm extending from the left upper quadrant to left mid- to lower quadrant. Urinalysis, complete blood count, and comprehensive metabolic panel show no evidence of renal or hepatic dysfunction. Given these findings, you decide to transfer him to a larger military treatment facility located nearby, where he is admitted for expedited evaluation. Furthermore, you place him in duties not to include flying status because, although his risk of developing sudden incapacitation, subtle performance decrement, or distracting symptoms is unknown, it is thought to be elevated based on the location of the mass, its size, and the differential diagnosis.

At the larger hospital, preoperative abdominal and pelvic CT scans show a 12.6 × 16.4 × 14 cm renal mass arising from the mid- to lower anterior aspect of the left kidney with mild left hydroureter. There is mass effect on the left renal vein and displacement of the adjacent colon, pancreas, and small bowel to the right. Additionally, there is extensive peripheral collateralization to systemic and portal vasculature, without evidence of other intra-abdominal organ involvement or adjacent lymphadenopathy. Chest CT shows no evidence of metastatic disease.

An uncomplicated left radical nephrectomy and adrenalectomy are performed. Intraoperatively, the surgeons find that they must dissect the plane between the pancreas and the tumor, as well as meticulously and circumferentially dissect out the tumor from the extensive collateralization, including a large number of tortuous gonadal vessels that are located inferiorly. The entire specimen is removed en bloc, including the left kidney, the renal mass, and the left adrenal gland. A single, mildly suspicious periaortic lymph node is also resected for pathological analysis.

Pathology examination reveals a large (12.6 × 16.4 × 14 cm) well-circumscribed mass in the lateral portion of the left kidney without apparent invasion or penetration of the renal capsule. A diagnosis of pT2bN0Mx succinate dehydrogenase (SDH) deficient type renal cell carcinoma (RCC) is made. The periaortic node is negative for metastatic disease.

**3. What is the most common presentation of RCC?**

A. Flank pain and hematuria.
B. Abdominal mass and varicoceles.
C. New onset seizure.
D. Incidental radiological finding in an asymptomatic individual.
E. A and C.

## ANSWER/DISCUSSION

**3. D.** With increased use of radiographic imaging for unrelated symptoms or conditions, the incidental diagnosis of RCC also increased.[11,16,27] Based on findings of a 2015 study, 25–30% of RCC diagnoses are made incidentally in patients who are asymptomatic with respect to their malignancy.[27] When symptoms are present, they may result from advanced localized disease or metastases. The "classic" clinical triad of RCC consists of hematuria, flank pain, and a palpable abdominal renal mass. However, only 10% of cases present with these features.[2,21,27] Scrotal varicoceles are detected in 2–10% of men with RCC, more commonly on the left side.[3] Varicoceles that fail to lessen in size when in a reclined position may suggest obstruction of the gonadal vein at the juncture of the renal vein by a renal tumor.[3] Other signs and symptoms of RCC include weight loss and invasion or mass effect on nearby intra-abdominal or retroperitoneal structures such as the inferior vena cava.[21] Compression or erosion of nearby blood vessels such as the inferior vena cava can lead to a variety of symptoms or complications, including lower extremity edema, thromboembolic events, or liver dysfunction.[21] Paraneoplastic syndromes may also develop in some individuals.[17] The most common sites of metastatic spread of

RCC are the brain, bone, liver, lymph nodes, and lung.[7,19,20] Signs and symptoms of disseminated disease vary based on the organ system(s) involved. All variations of RCC are classified based on the tumor, node, metastasis staging system.[13]

**4. What are some paraneoplastic syndromes that can occur in patients with RCC?**

A. Anemia and fever.
B. Polycythemia.
C. Coagulopathy and hypertension.
D. Hypercalcemia.
E. All of the above.

## ANSWER/DISCUSSION:

**4. E.** Paraneoplastic symptoms may be the initial and most conspicuous manifestation of RCC, and they may also herald disease recurrence. Heterogeneous syndromes may develop as the result of incompletely understood pathophysiological mechanisms. Altered immunological responses to neoplastic cells or the ectopic manufacture of different proteins or hormones play a role in the development of paraneoplastic disease.[8,17] The most common paraneoplastic effect in patients with RCC is hypercalcemia. Other possible paraneoplastic manifestations of RCC include hypertension, polycythemia, nonmetastatic hepatic dysfunction, galactorrhea, Cushing's syndrome, alterations in glucose metabolism, amyloidosis, anemia, neuromyopathies, vasculopathy, nephropathy, coagulopathy, prostaglandin elevation, cachexia, weight loss, and fever.[17] Nephrectomy is the most effective treatment for these syndromes, but they may return with recurrence of malignant disease.

SDH, a critical enzyme complex composed of multiple subunits, is involved in both the Krebs cycle and electron transport chain.[19] Thus its function is key to cellular metabolism. Loss of this enzyme results in crucial compromise of oxidative phosphorylation and aerobic metabolism.[23] Germline mutations in any one of several proteins of the SDH complex are linked to increased risk of hereditary renal cancer, paragangliomas and pheochromocytomas (PGL/PCC), and GI stromal tumors.[10,19,23] The inheritance pattern is autosomal dominant, with incomplete penetrance and a slight male predominance.[7,18] The SDH subtype of RCC is rare, with an estimated incidence of 0.05–0.2% of all RCCs.[7] Carriers of an SDH mutation tend to develop tumors at a younger age, with an average age of initial presentation between 33–39 yr.[7,19] At initial presentation, tumors that were confined to the kidney measured 5 cm on average.[7] SDH-deficient RCC can present aggressively and can metastasize, with the potential of late metastasis (occurring more than 5 yr after initial presentation).[7] Due to its rarity, there is a paucity of information regarding SDH-deficient RCC, with limited reported cases in the literature. Little is known about the character and location of these tumors, or their propensity for recurrence or metastasis. Likewise, their prognosis, morbidity, and mortality, as well as recommendations for their management and screening, are not clear.[18,19] Some studies indicate that low-grade tumors (T1/T2) rarely metastasize and are curable by surgical resection (with wide surgical margins).[19,24] Tumors that are inoperable or metastatic may be treated with chemotherapy, radionuclide therapy, or radiotherapy; responses to these treatments are variable.[24] Several studies propose posttreatment surveillance strategies to monitor for the development of kidney cancer, PGL/PCC, GI stromal tumors, pulmonary chondroma, and pituitary adenoma.[7,19] However, these surveillance practices are not standardized and there is no consensus guideline. Reasonable surveillance might include annual measurement of urinary or plasma metanephrines, annual abdominal MRI, and MRI of the pelvis, thorax, and neck every other year.[14,19,22–24] These specific tests and intervals are largely based on expert opinion.

Your patient's postoperative course is relatively unremarkable. His oncologist concludes that there is no indication for radiation therapy or chemotherapy. He recommends maintenance of good blood pressure control and a close follow-up schedule for the next 5 yr, adhering to NCCN guidelines for postnephrectomy surveillance of stage II and III kidney cancer. However, due to the fact that the NCCN guidelines do not take into consideration the unique risks associated with SDH-deficient RCC, he additionally recommends the following: annual MRI of the neck, chest, abdomen, and pelvis (to screen for new tumor development) and annual measurement of either free metanephrines or 24-h urine fractioned metanephrines (to screen for development of PGL/PCC). Finally, he encourages your aviator to consider subspecialty consultation at a center of excellence for SDH-deficient RCC.

At a 3-mo postoperative clinical evaluation, your patient is not experiencing any difficulties or limitations in activities of daily living. He reports that he is eating a normal diet and that his activity and exercise levels are at his baseline. He denies any GI symptoms, flank pain, or abdominal pain. Blood pressure is at goal and renal function is stable. Additionally, his surveillance imaging studies (chest/abdominal CT) are free of evidence of recurrent or metastatic disease. He undergoes a Medical Evaluation Board and is returned to military duty with an Assignment Limitation Code C-2. He returns to ground-based duties.

**5. What are some considerations of aeromedical decision-making in the case of rare diseases with poorly defined potential risks?**

A. Analyze the limited data available data considering only the reassuring features.
B. Rely on high-quality prognostic evidence to estimate future risks of medical complications that could impact flight safety.
C. Universally deny waiver consideration for the disqualifying condition(s) when there is unquantifiable risk.
D. Imprudently apply expert opinion to sparse clinical information.

## ANSWER/DISCUSSION

**5. B.** The rarity of SDH-deficient RCC and the sparsity of data pertaining to this condition result in unquantifiable risk. One approach to aeromedical decision-making in such circumstances is to universally deny waiver consideration for the disqualifying condition, assuming that unquantifiable risk equates to unacceptably high risk. However, in this unique case, a careful analysis of the limited available data was performed. Factors that were taken into consideration included the low grade of the tumor at time of diagnosis and resection, suggesting a

more favorable prognosis. Additionally, the achievement of a surgical cure through complete resection of the mass with negative margins and an intact renal capsule was considered positively. Other reassuring features included the absence of current residual or metastatic RCC, other primary tumors, or PGL/PCC. In light of expert recommendations suggesting an interval of 1–2 yr between screening is adequate to detect new tumors or PGL/PCC development, the short-term risk of a suddenly incapacitating complication or distracting symptoms arising prior to medical detection was considered to be low, provided the aviator complied strictly with the advised schedule of clinical, laboratory, and radiographic surveillance. In review, standards of aeromedical decision-making rely heavily on high-quality prognostic evidence to estimate future risks of medical complications that could impact flight safety. This case demonstrates a unique situation in which expert opinion was cautiously applied to limited clinical data to reach an estimated short-term risk threshold considered compatible with continued aviation duties.

## AEROMEDICAL DISPOSITION

Aeromedical concerns associated with RCC include the risks that arise from the symptoms or complications of the primary malignancy, the risks of potential paraneoplastic syndromes, and the risks engendered in the event of metastatic involvement. In the case of a primary presentation of a new diagnosis of RCC, risks vary based on stage of disease (early vs. advanced). With advanced or recurrent malignancy, the most common sites of metastatic involvement are the lungs, bones, liver, brain, and, in the case of recurrent disease after surgical resection, the renal fossa.[7,19] The initial presenting finding of metastases to the brain may include an acute seizure, severe headache, altered cognition or behavior, or a focal neurological symptom, all of which may lead to sudden incapacitation if occurring during flight. Bone metastasis can result in pathological fractures, which may lead to distracting or incapacitating pain.[7] Additional aeromedical concerns include the early and late side effects of treatment, whether chemotherapy, surgery, or radiation. A diagnosis of RCC is disqualifying for flying in all branches of the U.S. military due to these concerns.

For trained aircrew, the U.S. Navy requires a mandatory waiting period of 2 yr after resection of stage I or stage II RCC provided there is no disease recurrence during this interval. Untrained aircrew with only one kidney are not eligible for waiver. The U.S. Navy waiver guide addresses the requirements needed for waiver submission.[14]

Members with stage I tumors have a good possibility of obtaining waivers according to U.S. Army waiver guidance. Individuals with more widespread disease may have an "unacceptable risk," driven by concerns for the development of central nervous system disease.[25] Like the U.S. Navy, untrained U.S. Army applicants with congenital or acquired absence of one kidney are not eligible for a waiver.

The U.S. Air Force Waiver Guide does not directly address renal cancer but does list it with other cancers that will require Medical Evaluation Board results and a thorough evaluation of a member prior to waiver consideration. To be eligible for a waiver, the cancer must be considered cured or in a state of remission. If the member received chemotherapeutics, treatment must be completed and adequate time elapsed to ensure resolution of any adverse effects. Cases are considered individually and must be reviewed by the U.S. Air Force Aeromedical Consultation Service prior to waiver disposition.[26]

The Federal Aviation Administration considers the diagnosis of renal cell carcinoma disqualifying for all flying classes under Title 14 of the Code of Federal Regulations Part 67. Renal cancer is a Condition AMEs [Aviation Medical Examiner] Can Issue (CACI). If the applicant meets all the acceptable criteria listed in the CACI worksheet, the AME can issue as a CACI-qualified renal cancer. If the applicant does not meet all of the acceptable criteria, the AME must defer to the Federal Aviation Administration to determine whether an airman is medically fit to fly.[4]

In the case of your pilot with a diagnosis of SDH-deficient RCC, a waiver request was submitted after 4 mo of postoperative surveillance. The waiver package and medical records were reviewed by the Aeromedical Consultation Service, which recommended a flying class II waiver for a duration of 1 yr, based on the aeromedical reasoning discussed above. Approximately 6 mo after the detection of the abdominal mass and completion of definitive treatment of the diagnosed RCC, this aviator returned to flying status.

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## REFERENCES

1. Cartwright SL, Knudson MP. Evaluation of acute abdominal pain in adults. Am Fam Physician. 2008; 77(7):971–978.
2. DeKernion JB. Real numbers. In: Walsh PC, Gittes RF, Perlmutter AD, editors. Campbell's urology. Philadelphia (PA): WB Saunders; 1986:1294.
3. El-Saeity NS, Sidhu PS. "Scrotal varicocele, exclude a renal tumour." Is this evidence based? Clin Radiol. 2006; 61(7):593–599.
4. Federal Aviation Administration. Decision considerations – aerospace medical dispositions. Item 41. G-U system. In: Guide for aviation medical examiners. Washington (DC): Federal Aviation Administration; 2015. [Accessed 8 Nov. 2018]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item41/amd/nd/renal.
5. Fowler KJ, Garcia EM, Kim DH, Cash BD, Chang KJ, et al. Palpable abdominal mass—suspected neoplasm. American College of Radiology. ACR Appropriateness Criteria. 2019. [Accessed 1 Apr. 2019]. Available from https://acsearch.acr.org/docs/69473/Narrative/.
6. Gammell S, Beattie DK, Thompson HH. Difficulties in the diagnosis of an intra-abdominal mass. Postgrad Med J. 1999; 75(887):559–561.
7. Gill AJ, Hes O, Papathomas T, Šedivcová M, Tan PH, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol. 2014; 38(12):1588–1602.
8. Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol. 1996; 14(4):216–222.

9. Grégoire S, Saloojee N. Abdominal mass. In: Thomson AB, Shaffer EA, editors. First principles of gastroenterology and hepatology: the basis of disease and an approach to management, 6th ed. Charleston (SC): CreateSpace Independent Publishing Platform; 2012:27–28.
10. Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis. 2014; 21(1):81–90.
11. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008; 113(1):78–83.
12. Mendelson R. Imaging for chronic abdominal pain in adults. Aust Prescr. 2015; 38(2):49–54.
13. National Comprehensive Cancer Network. NCCN guidelines. [Accessed 17 Nov. 2018]. Available from https://www.nccn.org/professionals/physician_gls/default_nojava.aspx.
14. Naval Aerospace Medical Institute. 9.8. Kidney tumors. In: U.S. Navy aeromedical reference and waiver guide. Pensacola (FL): Naval Aerospace Medical Institute; 2018. [Accessed 1 Dec. 2018]. Available from https://www.med.navy.mil/sites/nmotc/nami/arwg/Pages/default.aspx.
15. Nguyen VX, Le Nguyen VT, Nguyen CC. Appropriate use of endoscopy in the diagnosis and treatment of gastrointestinal diseases: up-to-date indications for primary care providers. Int J Gen Med. 2010; 3:345–357.
16. O'Connor SD, Pickhardt PJ, Kim DH, Oliva MR, Silverman SG. Incidental finding of renal masses at unenhanced CT: prevalence and analysis of features for guiding management. AJR Am J Roentgenol. 2011; 197(1):139–145.
17. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. Rev Urol. 2002; 4(4):163–170.
18. Raygada M, King KS, Adams KT, Stratakis C, Pacak K. Counseling patients with succinate dehydrogenase subunit defects: genetics, preventive guidelines, and dealing with uncertainty. J Pediatr Endocrinol Metab. 2014; 27(9–10):837–844.
19. Ricketts CJ, Shuch B, Vocke CD, Metwalli AR, Bratslavsky G, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol. 2012; 188(6):2063–2071.
20. Shvarts O, Lam JS, Kim HL, Han KR, Figlin R, Belldegrun A. Eastern Cooperative Oncology Group performance status predicts bone metastasis in patients presenting with renal cell carcinoma: implication for preoperative bone scans. J Urol. 2004; 172(3):867–870.
21. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer. 1971; 28(5):1165–1177.
22. Srirangalingam U, Walker L, Khoo B, MacDonald F, Gardner D, et al. Clinical manifestations of familial paraganglioma and pheochromocytomas in succinate dehydrogenase B (SDH-B) gene mutation carriers. Clin Endocrinol (Oxf). 2008; 69(4):587–596.
23. Tong WH, Sourbier C, Kovtunovych G, Jeong SY, Vira M, et al. The glycolytic shift in fumarate-hydratase-deficient kidney cancer lowers AMPK levels, increases anabolic propensities and lowers cellular iron levels. Cancer Cell. 2011; 20(3):315–327.
24. Tufton N, Shapiro L, Srirangalingam U, Richards P, Sahdev A, et al. Outcomes of annual surveillance imaging in an adult and pediatric cohort of succinate dehydrogenase B mutation carriers. Clin Endocrinol (Oxf). 2017; 86(2):286–296.
25. U.S. Army Aeromedical Activity. Kidney tumors (ICD9 189.0). In: Flight surgeon's aeromedical checklists. Aeromedical policy letters. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2014. [Accessed 2 Oct. 2018]. Available from https://glwach.amedd.army.mil/victoryclinic/documents/Army_APLs_28may2014.pdf.
26. Van Syoc D. Cancers (misc.) (Jan. 16). In: Air Force waiver guide. Wright-Patterson AFB (OH): U.S. Air Force School of Aerospace Medicine; 2019:138–140.
27. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015; 67(3):519–530.