Chapter 8
Genitourinary Sites

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SBRT for Clinically Localized Prostate Cancer

Checklist

- **H&P**: Urinary (AUA) symptoms, history of inflammatory bowel or connective tissue disorder, prior RT, prior TURP, comorbidity (e.g., dementia, severe tremor, cardiac comorbidity), pacemaker status, erectile function, bone pain, family history, DRE.
- **Labs**: PSA. For intermediate- to high-risk patients who may receive androgen deprivation (ADT), testosterone, and baseline LFTs.
- **Tissue**: TRUS-guided biopsy with 12 or more cores. MRI-fusion biopsy is ideal especially if suspicious

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lesion(s) not sampled. Assessment of percent of + biopsies (% + Bx) and Gleason score (GS) critical. Establish T stage, and assess the presence of large median lobe.

Indications and Workup

- **Low risk**: PSA < 10, GS 6, T1-T2a. Ten-year prostate cancer-specific mortality (PCSM) ~1–2%:
  - Imaging not indicated for workup
  - Favor management via active surveillance, but RP, EBRT, BT, and SBRT are considered appropriate options for selected patients. ADT not indicated.
- **Favorable intermediate risk (IR)**: Any single IR factor (T2b-2c, GS 7, PSA 10–20) and <50% biopsy cores positive (low volume disease). Ten-year PCSM ~5%:
  - Bone imaging not routinely recommended per NCCN guidelines.
  - Pelvic CT or MRI indicated if >10% pelvic nodal risk.
  - Growing evidence for the role of genomic testing for risk stratification but little evidence involving patients treated with SBRT.
  - Treatment is favored; RP, EBRT, BT, and SBRT provide comparable outcomes. Short-term (ST) ADT (4 months) with RT should be considered (especially for favorable IR patients on a case-by-case basis, but excellent outcomes with monotherapy have been reported).
- **Unfavorable IR**: More than one IR factor (T2b–2c, GS 7, PSA 10–20), or GS 4 + 3 disease, or ≥50% of cores positive (high-volume disease). Eight–ten-year PCSM ~5–10%:
  - Bone imaging favored (NM bone scan, NaF PET/CT, or PSMA PET).
  - Pelvic CT or MRI indicated if >10% pelvic nodal risk.

- Treatment indicated; RP, EBRT+ ST ADT, and SBRT provide excellent outcomes. Combination BT + EBRT or SBRT+EBRT are believed to yield higher control rates. ST ADT with RT (4 months) recommended; however, SBRT±ADT well studied.

- **High risk**: PSA > 20, T3–4, GS ≥ 8, 8–10-year PCSM ~10–20%. Very high risk = T3b/4 or primary Gleason 5, or 2+ high-risk factors, or >4 cores with GS8+ disease:
  - Bone imaging and pelvic imaging required.
  - Molecular imaging is useful for staging if available (PSMA, fluciclovine/Axumin) and has been studied in a prospective randomized trial:
    - ProPSMA (Hofman et al. 2020): *N* = 302. High-risk PCa, PSMA PET/CT vs. conventional staging. PSMA was 27% more accurate and changed management 27% of the time versus 5% of the time with conventional staging.
  - Treatment indicated: Favor combination BT + EBRT or SBRT+EBRT with long-term ADT (18–24 months). Prostate-only SBRT is not well studied in this setting and should not be offered off-trial except in extenuating circumstances. For very-high-risk patients, consider referral to medical oncology for discussion of next-generation anti-androgen therapy or chemotherapy (STAMPEDE (Attard et al. 2022), RTOG 0521 (Rosenthal et al. 2019)).

Simulation

- **Fiducial markers**: Recommend TRUS-guided placement of at least three fiducial markers at least 1 week prior to CT simulation (to allow for markers to "settle"). If fiducial tracking with orthogonal X-ray is planned, markers should ideally be at least 2 cm apart (e.g., 2 markers in the base and 1 in the apex).

- **Rectal spacer**: At the UCSF, hydrogel rectal spacer placement is not routinely recommended, as evidence for its clinical benefit is controversial (Hall et al. 2021).
- **Simulation**: Enema on the day of simulation. For robotic SBRT at the UCSF, we simulate with empty bladder due to prolonged treatment time, and full bladder for LINAC SBRT. For combined EBRT+SBRT, simulate with full bladder for EBRT portion. Simulate with alpha cradle or vac-bag for SBRT:
  - At the UCSF, we perform MRI simulation on the same day in the treatment position with a flat patient table.

Contouring, Treatment Planning, and Image Guidance

- **Urethra delineation**: Fusion of MRI/CT images is accomplished by aligning the gold seeds best seen on "3D VIBE T1-weighted gradient echo," or "susceptibility-weighted imaging (SWI)" MRI sequences, to the seeds on CT in order to facilitate accurate delineation of the urethra identified on T2 MRI sequences onto the CT images for treatment planning. If MRI is contraindicated, CT urethrogram at simulation is used to define the urethra.
- **Contouring**:
  - GTV: any lesion visible on MRI, areas of ECE or SVI.
  - CTV: prostate, and proximal 0–20 mm of seminal vesicles, depending on the risk level of the patient for seminal vesicle invasion (SVI). If gross SVI is present, they are incorporated into the target, while carefully sparing nearby bowel, rectum, or bladder.
  - PTV: two common regimens are used at the UCSF based on physician preference:

- 38 Gy in 4 fractions (or 19 Gy in 2 fractions as a boost), CTV + 2 mm, 0 mm expansion to spare rectum posteriorly.
- 36.25 Gy in 5 fractions to PTV (40 Gy to the prostate volume), CTV + 3–5 mm, reduced posteriorly.

- Contour should include the penile bulb and urethra (avoidance structures; include portions of the membranous urethra extending into the bulb, and the bladder neck), femurs, rectum, nearby large bowel and small bowel.
- Double-check MRI-CT fusion and view contours (axial, sagittal, and coronal images) to ensure that they are reasonable, particularly on the simulation CT.

- **Prescription, schedule, and dose constraints**:
  - Monotherapy:
    - 38 Gy in 4 fractions (Jabbari et al. 2012) to PTV, V100% ≥ 95%:
      - Rectum Dmax ≤ 100%, V75% < 1 cc; bladder Dmax Dmax ≤ 100%, V75% < 2 cc; urethra 0.1 cc Dmax<120%; prostate V150% < 50% (limit heterogeneity); bowel Dmax ≤ 28 Gy.
    - 36.25 Gy in 5 fractions to PTV, 40 Gy to the prostate volume and areas of GTV (Meier et al. 2018; Zaorsky et al. 2020):
      - Rectum V36Gy < 1 cc (up to 2 cc); bladder V40 < 2 cc, V37Gy < 5–10 cc; prostatic urethra V47Gy < 20%; bowel V30Gy < 1 cc; bulb D2% < 28.5 Gy.
  - Boost:
    - 19 Gy in 2 fractions (Chen et al. 2021) to PTV, V100% ≥ 95%:
      - Dose constraints identical to above 38 Gy/4 fx, and TG 101.
      - Pelvic IMRT can precede or follow boost within 2 weeks; typical dose is 45 Gy in 25 fractions. Ideally, a composite plan is created to

ensure no hotspots in OARs. Pay attention to ureters.
- 21 Gy in 3 fractions has been reported elsewhere (Kim et al. 2020).

- **Image guidance**:
  - Cyberknife®:
    - Many published studies have utilized Cyberknife®, with intra-fraction fiducial tracking capability utilizing orthogonal kV X-ray.
  - Gantry-mounted LINAC:
    - LINAC-based SBRT appears to be as safe and efficacious (Dang et al. 2020). Series with intra-fraction reimaging (3× per fraction, Kishan et al. 2019; or up to every 15–30 s with BrainLab® or other real-time tracking system) and without (D'Agostino et al. 2016) have been reported.
- **Treatment considerations**:
  - Consider daily enema, as per RTOG 0938, although our practice has not been to use daily enemas; patients are encouraged to void prior to each RT session.
  - Consider every other day treatment (typical practice at the UCSF), or twice-weekly treatment (based on low-level evidence for possibly lower acute toxicity).
- **Toxicity**:
  - Acute:
    - Genitourinary (mild-moderate: ~30–50%): Urinary frequency and urgency, worsened obstructive symptoms, usually mild to moderate.
      - Management: Tamsulosin or other alpha-blocker, ibuprofen PRN, pyridium OTC PRN for dysuria (obtain UA to rule out UTI), step-up to a short steroid burst (e.g., methylprednisolone dose pack [Medrol Dosepak®]) only if severe symptoms or nearing obstruction. Monitor for urinary obstruction, although rare (<1–3%).

- Gastrointestinal (mild-moderate: ~10–20%): Diarrhea, rarely proctitis, hematochezia.
  - Management: Low-residue diet and anti-diarrheals as needed. ProctoFoam or rectal sucralfate or rectal amifostine can be used for moderate-to-severe proctitis. Hematochezia often a result of aggravated hemorrhoids, but always requires careful history and workup. Biopsy of the rectal mucosa is contraindicated for at least 6 months after radiation and can lead to severe complications.

- Late:
  - Rates of grade 3+ GU/GI toxicity on SBRT monotherapy are <1–3% in a meta-analysis of the literature (Jackson et al. 2019).
    - Rates of grade 3+ GU/GI toxicity are <5%/2% for SBRT boost (Chen et al. 2021).
  - Radiation cystitis, hemorrhagic cystitis, urethral stricture, rectal ulcer, and fistula have been reported:
    - Hyperbaric oxygen can be an effective treatment for late radiation-related toxicities such as cystitis and proctitis. Refer to a certified medical hyperbaric oxygen center staffed with a pulmonologist.
  - Late grade 1 or grade 2 microscopic or macroscopic hematuria is not uncommon (~5–10%), and may require cystoscopy to rule out other causes (e.g., bladder cancer).
  - Erectile dysfunction is similar to conventional and hypofx prostate RT.
  - Factors that may increase late toxicity: prior TURP (ensure accurate avoidance structure contour of the entire TURP defect to avoid hotspots), inflammatory bowel disease, and attempts to cover a large median lobe.

Follow-Up

- Per NCCN v3.2020, PSA every 6–12 months for 5 years, then annually thereafter. DRE annually can be omitted if PSA undetectable.
- Phoenix definition of biochemical recurrence is PSA >2 ng/mL above the PSA nadir:
  - Can consider workup earlier if clear rising PSA on three consecutive tests and based on PSA doubling time.
- PSA bounce (10–20% of patients) can be observed between 6 months and 3 years after SBRT and is usually a "benign" finding.

Evidence

SBRT Monotherapy

- **Pooled meta-analysis** (Jackson et al. 2019): 38 studies with 6116 patients, median f/u of 39 months; 78% of studies included intermediate risk, 38% of studies included a small number of high-risk patients ($N = 470$ pts). Median dose was 7.25 Gy × 5 fractions. Pooled 5-year biochemical control (BC) of 95.3%. Acute/late grade 3+ GU toxicity was 0.5%/2%. Acute/late grade 3+ GI toxicity was 0.06%/1.1%.
- **Pooled multi-institutional data with 7-year results** (Kishan et al. 2019): Ten institutional phase II and two multi-institutional phase II trials were pooled, $N = 2142$ men, 55.3% low risk, 32.3% favorable intermediate risk, 12.4% unfavorable intermediate risk, with median f/u of 6.9 years. Variety of doses (33.5 Gy/5 to 40 Gy/5, 69% Cyberknife). Seven-year biochemical recurrence: 4.5% for low-risk, 8.6% for favorable intermediate-risk, and 14.9% for unfavorable intermediate-risk patients. Seven-year cumulative incidence of grade 3+ GU/GI toxicity was 2.4%/0.4%.

- **HYPO-RT-PC, Phase III RCT, Denmark** (Widmark et al. 2019): *N* = 1200 patients, tested 78 Gy/39 vs. 42.7 Gy/7 in non-inferiority trial of mostly intermediate-risk (89%) patients. ADT was not allowed. Only ~6% of patients had Gleason 8+, and median PSA was 8.7. SBRT was delivered with a mix of 3D-CRT (80%), IMRT, and VMAT with fiducials. With a median f/u of 5.0 years, SBRT was non-inferior to EBRT (5-year failure-free survival of 84% vs. 84%, HR 1.002, *P* = 0.99). SBRT had slightly higher acute GU toxicity (28% vs. 23%, grade 2+), but equivalent late toxicity (5% vs. 5%). HRQOL showed higher acute GU/GI symptoms for SBRT, but no difference in late symptoms.
- **PACE-B, Phase III RCT, UK/Canada** (Van As et al. 2019; Tree et al. 2022): *N* = 874 patients, 91% intermediate risk, no high risk. 36.25 Gy in 5 fractions (40 Gy to prostate) mostly with Cyberknife, versus conventional or moderate hypofractionated RT (most common 78 Gy/39 and 62 Gy/20). No ADT was allowed. Acute RTOG grade 2+ GU toxicity was 23% for SBRT and 27% in the EBRT arms. Acute RTOG grade 2+ GI toxicity was 10% for SBRT and 12% for EBRT. In the study appendix, CTCAE acute GU toxicity appears numerically higher for SBRT (grade 1–2), as were the rates of grade 1–2 diarrhea and proctitis. SBRT symptoms peaked earlier after radiation (2–4 weeks) compared to EBRT (4–6 weeks). Two-year toxicity outcomes showed RTOG grade 2+ GU toxicity in 3% of SBRT and 2% of EBRT patients, and grade 2+ GI toxicity in 3% of SBRT and 2% of EBRT patients. No RTOG grade 4 or higher toxicity was observed at 2 years. Biochemical control and other oncologic endpoints are not yet available but expected to be reported in the next few years.
- **Phase I dose escalation 5-year results, MSKCC** (Zelefsky et al. 2019): *N* = 136 patients, 32.5 Gy, 35 Gy, 37.5 Gy, and 40 Gy/5 fx. Dose escalation was well toler-

ated. There was a dose-response pattern for greater low-grade toxicity with higher dose. One grade 3 GU toxicity occurred in the 40 Gy arm (stricture). Five-year PSA failure was 15% for 32.5 Gy/5 and 0% for 37.5 Gy and 40 Gy. Rates of 2-year posttreatment biopsy positivity were 47.6%, 19.2%, 16.7%, and 7.7%, for the dose arms. Interestingly, rates of biopsy positivity were higher than PSA failure rates.

- **PSA nadir after SBRT monotherapy versus LDR/HDR brachytherapy** (Levin-Epstein et al. 2020): $N = 3502$ patients, median f/u of 72 months. 63.5% low risk, 11.7% unfavorable intermediate risk. Nadir PSA was median of 0.2 for SBRT monotherapy at a median of 44 months, between 0.1 and 0.2 for HDR at a median of 37 months, and 0.01–0.2 for LDR at a median of 51 months. There was no difference in biochemical control or rate of PSA <0.4 at 4 years.
- **Key points**: Long-term outcomes are beginning to emerge for SBRT monotherapy for low- to intermediate-risk prostate cancer (Cushman et al. 2019), as well as early results from two phase III studies, HYPO-RT-PC and PACE-B. SBRT can deliver excellent 5–7-year biochemical control rates of 90–95%, with low rates of grade 3+ toxicity of 1–3%. Further study is needed as to optimal treatment for unfavorable intermediate-risk patients, including questions of dose, +/− ADT, and +/− pelvic RT. There is still very limited evidence for SBRT for high-risk patients.

SBRT Boost

- **Georgetown experience** (Paydar et al. 2017; Mercado et al. 2016): $N = 108$ patients with a median f/u of 4.4 years, retrospective review. 54.6% high risk. 19.5 Gy/3 fractions with Cyberknife, plus pelvic IMRT (45–50.4 Gy). Three-year biochemical control was 100%/89.8% for intermediate/high-risk patients.

Toxicity was reported separately; late grade 3+ GU toxicity was 6%, and late grade 3+ GI toxicity was 1% (telangiectasia treated with hyperbaric oxygen). 7% of men had late rectal bleeding.

- **Multi-institutional pooled safety data** (Kaplan et al. 2020): *N* = 473 patients, retrospective analysis. A variety of doses were used, median 19.5 Gy (fractions not reported). With a median f/u of 33 months, grade 3 GU toxicity was 3.2%, with no grade 4. Grade 3+ GI toxicity was 2.1%.
- **Phase I trial, Asan Medical Center, Republic of Korea** (Kim et al. 2020): *N* = 26 patients, 100% high risk (mostly very high). Prospective phase I/IIa study. 44 Gy pelvic RT, plus 18 vs. 21 Gy in 3 fractions on Cyberknife. 0% G3+ GU/GI toxicity at a median f/u of 35 months. Three-year biochemical control was 88.1%, with no difference between doses.
- **UCSF experience** (Chen et al. 2021; Anwar et al. 2016): Retrospective analysis of *N* = 131 men treated with SBRT boost (19 Gy/2, Cyberknife) plus 45 Gy/25 pelvic IMRT, with a median f/u of 73.4 months. *N* = 101 men treated with HDR boost (19 Gy/2) were used as a comparison. 68.8% of men had high-risk and 26.0% unfavorable intermediate-risk disease; 95% received ADT. Five-year biochemical control (BC) was 88.8% and 91.8% for SBRT and HDR boost. There was no difference in BC or metastasis freedom (5-year 91.7% vs. 95.8%) between SBRT and HDR boost on multivariate analysis or after propensity matching. Grade 3+ GU/GI toxicity was 4.6%/1.5% for SBRT boost. Stricture was not observed in SBRT boost patients and was seen in 1 HDR boost patient. Local failure was 1.7% overall (but low biopsy rate); most recurrences were bone or non-pelvic nodal. Median PSA nadir for SBRT boost was 0.088.
- **Key points**: For unfavorable or high-risk patients, SBRT boost with ADT may offer a safe and effective alternative for those unable/unwilling to receive HDR/

LDR boost. The data is not as robust as for SBRT monotherapy but are accumulating. Data from the brachytherapy boost literature has yet to show a survival advantage to boost therapy but does show a biochemical control advantage over conventional radiation. Comparative trials of SBRT and brachytherapy boost are warranted and ongoing.

SBRT for Prostate Cancer: Oligometastasis-Directed Therapy

Oligometastatic Prostate Cancer

- **Key points:**
  - As the availability of molecular imaging increases, more patients with "oligometastatic" or "oligorecurrent" prostate cancer are likely to be identified. There remains no universally agreed-on definition for "oligometastatic disease." Frequently used definitions limit the number of metastasis to ≤3 or ≤5 extracranial metastases (APCCC 2019 (Gillessen et al. 2020)).
  - For the purposes of accessing prognosis and for management, we find it useful to divide patients into those with "synchronous" (presenting with metastatic disease) vs. "metachronous" (subsequently developed) metastatic disease. Patients with "synchronous oligometastatic" tend to have a worse prognosis, behaving more as the classical metastatic and being at risk for diffuse and/or rapid progression. It is possible that when "oligometastasis" is detected, there is more disease that cannot be detected, i.e., the "tip of the iceberg." In contrast, most of the trials conducted to date (described below) have focused on patients with "metachronous" metastatic disease.

- It is also useful to classify "high-volume" disease metastatic disease as defined in the CHAARTED study: "the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis …," which has become accepted as a way to describe patients for whom aggressive management (e.g., local treatment) is less likely to be of benefit. Notably, staging in this study was based on conventional, not molecular, imaging. It is important to keep in mind that the number of metastases detected is a function of the sensitivity of imaging modalities used and the volume of disease (and PSA level).
- The appropriate clinical goal of oligometastasis-directed therapy is also yet to be fully defined. Thus far, some studies have focused on non-survival endpoints such as ADT freedom, castrate resistance freedom, and progression freedom. The true rate of "cure" with oligometastasis-directed therapy is unknown but is likely low.
- Further study is needed, and patients should be enrolled on clinical trials of oligometastasis-directed therapy whenever possible.
- Because of the potential of harm with high-dose radiation involved in SBRT, diligent care and clinical judgment must be exercised and an individualized approach to minimize the risk of toxicity depending on body site treated is critical. In particular, SBRT to visceral organs such as lung, abdominal sites close to bowel, and liver can occasionally lead to serious, life-threatening toxicity.

Evidence

- **STOMP, phase II randomized trial** (ASCO 2020 (Ost et al. 2020)): $N = 62$ patients, ≤3 mets by choline-PET, randomized to SBRT/surgery to all sites dz. (met-

directed therapy, MDT) vs. observation. SBRT dose was 30 Gy/3 fx; most common surgery was salvage pelvic lymph node dissection (PLND). 54.8% of patients had nodal disease only, and 45.2% had non-nodal (almost all bones). Median f/u 5.3 years, 5-year ADT-free survival 34% in MDT arm vs. 8% in obs. Five-year castrate resistance freedom 76% for MDT vs. 53% for obs.

- **POPSTAR, prospective single-arm trial** (Siva et al. 2018a): N = 33 patients, 1–3 mets by NaF PET/CT + conventional imaging, tx with 20 Gy × 1 (80% isodose) SBRT to all sites of dz. 60.6% bone-only disease. Two-year LC was 93%, and 2-year disease PFS was 39%. Two-year ADT freedom was 48%. 3% (N = 1) grade 3 toxicity (vertebral fracture).
- **ORIOLE, phase II randomized trial** (Phillips et al. 2020): N = 54 patients, 1–3 mets (metachronous), no ADT within 6 months and <3 years total, randomized to SBRT MDT vs. observation. PSMA performed but physicians blinded. At 6 months, 19% of SBRT patients progressed (PSA/imaging/ADT initiation) vs. 61% of observed patients. No grade 3+ toxicity. If all PSMA-avid lesions were targeted, progression was lower (16% vs. 63%).
- **Elective nodal RT vs. SBRT for nodal oligorecurrence** (De Bleser et al. 2019): N = 506 patients (309 SBRT, 197 nodal RT [ENRT]), multi-institutional retrospective analysis, with 1–5 nodal oligorecurrence. Median f/u 36 months. Only 8% had prior WPRT, and median PSA at recurrence 2.7. 72% had pelvic nodal oligorecurrence. Pelvic ENRT led to fewer nodal recurrences (20% vs. 42%) due to reduction in pelvic recurrence (1.5% vs. 17.8%). No statistically significant difference in distant nodal, bone, or visceral mets. Three-year castrate resistance freedom was equivalent (88% vs. 87%). Grade 3+ toxicity was 0% for SBRT and 2.5% for ENRT (P = 0.009).

- **Safety evidence:**
  - **UK prospective observational trial** (Chalkidou et al. 2021): *N* = 1422 stage IV patients of all primary cancer types (28.6% prostate), 1–3 extracranial metachronous mets (at least 6 months between primary and met development), SBRT 24–60 Gy in 3–8 fx. No treatment-related deaths with median f/u of 13 months. Most common grade 3+ toxicity was fatigue (2%) and elevated liver enzymes (0.6%). One-year OS was 92.3%.
  - **Meta-analysis of prospective trials** (Lehrer et al. 2021): *N* = 943 patients (21 trials) with mixed primary histologies, with ≤5 mets. Acute grade 3+ toxicity was 1.2%, and late grade 3+ toxicity was 1.7%. One-year LC was 94.7%, and 1-year OS was 85.4%. Serious toxicities often involved lung, liver, and bowel.

SBRT for Renal and Adrenal Tumors

SBRT for Renal Cell Carcinoma (RCC)

- **Key points:**
  - Small renal masses (<4 cm) are increasingly identified incidentally on imaging.
  - Traditional signs/symptoms of hematuria, flank pain, and flank mass are typically present for more advanced RCC, and many early-stage RCCs present asymptomatically or with painless hematuria.
  - While the majority of small renal masses are benign, some harbor early-stage RCC:
    - Differential includes RCC, metastasis, lymphoma, abscess, or benign lesions such as oncocytoma, angiomyolipoma, metanephric adenoma, and simple cysts.

- Management of early-stage RCC (T1a–T1b, <4 cm vs. 4–7 cm) should involve a multidisciplinary evaluation including a urologist:
  - Management can include active surveillance, biopsy, partial nephrectomy, or, for inoperable patients, interventional radiology ablation or SBRT.
- There is growing evidence for the efficacy and safety of SBRT for the treatment of early-stage, kidney-confined RCC:
  - Care should be taken for lesions near the renal pelvis and ureter. Comparatively less is known about the safety of SBRT in these areas.
  - Doses most commonly reported include 24–26 Gy in 1 fraction, 40 Gy in 5 fractions, and 42 Gy in 3 fractions. At the UCSF, we favor biopsy for tissue confirmation and fiducial placement for Cyberknife fiducial tracking when feasible.
  - Limiting the high-dose spill (>50% isodose volume) to normal kidney has been suggested to help limit the risk to kidney function.
- Despite having a reputation for being radioresistant, SBRT for both primary and metastatic RCC tumors can achieve good local control and tumor response.

Evidence

- **Meta-analysis of SBRT for RCC** (Correa et al. 2019a): $N = 372$ patients, 26 studies (11 prospective). 26 Gy × 1 or 40 Gy/5 fx was the most common fractionation. Pooled local control was 97.2%, and tumors were generally 2–5 cm, with some studies treating larger, T1b tumors. Tissue confirmation of RCC was obtained in 78.9% of patients. Grade 3–4 toxicity was 1.5%, and change in eGFR was −7.7 mL/min (95% CI −12.5 to −2.8). These toxicities compare favorably to IR abla-

tion. 2.9% of patients (with preexisting renal failure) went on to require dialysis.

- **SBRT for RCC in solitary kidney** (Correa et al. 2019b): $N = 81$ patients with solitary kidney, underwent SBRT for RCC (histologically confirmed in 91%), median tumor size was 3.7 cm, and 37% were larger than 4 cm. Median dose was 25 Gy/1 fraction. With median 2.57 years' f/u, 2-year LC was 97%, PFS was 77.5%, and cancer-specific survival was 98.2%. Median eGFR decline after SBRT was only −5.8 ± 10.8 mL/min. No patients went on to require dialysis.
- **Pooled multi-institutional retrospective analysis** (Siva et al. 2018b): $N = 223$ patients, median f/u 2.6 years, mean tumor size 4.4 cm, most patients got 25 Gy × 1 or 40 Gy/5 fx. Grade 3–4 toxicity rate was 1.4%. Two-year local control was 97.8%, cancer-specific survival was 95.7%, and PFS was 77.4%. Mean decrease in eGFR was −5.5 ± 13.3 mL/min.
- **SBRT for T1b (>4 cm) RCC** (Siva et al. 2020): $N = 95$ patients, median f/u 2.7 years, 78% inoperable. 0% grade 3–5 toxicity. Median dose was 26 Gy in 1 fraction, but ~49% received multi-fraction. Two-year local failure was 2.9%, 2-year CSS was 96.1%, and PFS was 81.0%. eGFR change was −7.9 ± 11.3 mL/min. 20% actually had an increase in eGFR. 17.8% without baseline CKD went on to meet CKD criteria during follow-up, but it was unclear what contribution SBRT had to this. Mean pre-SBRT eGFR was 57.2 mL/min, consistent with grade 3 CKD. 3.2% of patients went on to require dialysis, a rate similar to those reported for partial nephrectomy and IR ablation; attribution to underlying CKD progression versus treatment effect is unclear.
- **SBRT dose and renal function decline** (Siva et al. 2016): $N = 21$ patients, GFR measured before and after SBRT with Cr-EDTA or Tc-99-DMSA SPECT. Greater GFR decline was reported for 26 Gy × 1 than 42 Gy/3 fx. The R50% conformality index seemed to also cor-

relate with GFR decline. The authors suggest sparing functional kidney from high dose (>50% isodose) to limit GFR decline.

- **SABR-ORCA, meta-analysis of SBRT for metastatic RCC** (Zaorsky et al. 2019): *N* = 1602 patients in 28 studies of SBRT for both extracranial and intracranial RCC metastases. Median treatment volume was 59.7 cc for extracranial mets and 2.3 cc for intracranial. One-year LC was 89% and 90% for extra/intracranial mets. One-year OS was 86.8% for patients with extracranial mets and 49.7% for those with intracranial mets. Grade 3+ toxicity was 0.7% for extracranial and 1.1% for intracranial disease. Authors conclude that SBRT was highly efficacious and safe for metastasis-directed therapy in RCC. Single-fraction tx and higher dose were associated with LC.

SBRT for Adrenal Gland Metastases

- **Key points:**
  - The adrenal glands are common sites for metastasis from non-small cell lung cancer, melanoma, renal cell carcinoma, and colon cancer.
  - When carefully performed, SBRT can achieve good rates of local control with low risk of toxicity. Care must be taken and an individualized approach to each patient's anatomy and nearby organs at risk, in particular bowel, stomach, liver, and kidney:
    - At the UCSF, 50 Gy in 5 fractions (BED-10 of 100 Gy) is a common fractionation, but the dose fractionation is individualized based on target size and nearby structures. Fiducial placement is preferred in order to facilitate robotic SBRT with intra-fraction fiducial tracking for image guidance:

- A 4D-CT approach with ITV ± abdominal compression or breath-hold/respiratory gating can also be used.

- Despite concern for adrenal insufficiency or hypertensive crisis, clinically significant adrenal insufficiency or hypertensive complications after SBRT to the adrenal gland are exceedingly rare. By comparison, IR ablation leads to significantly higher complication rates including adrenal insufficiency and intra-procedural hypertensive crisis (Pan et al. 2020).

Evidence

- **Meta-analysis of SBRT for adrenal metastases** (Chen et al. 2020): $N = 1006$ patients in 39 retrospective studies with median f/u of 12 months. $N = 63$ patients with bilateral adrenal mets were treated. Median BED-10 was 67 Gy, and median dose was 38 Gy in 5 fx. Pooled 1-year and 2-year LC rates were 82% and 63%, and 1-year and 2-year OS rates were 66% and 42%. A strong relationship between BED-10 and LC was found, and BED-10 of 100 Gy was predicted to correspond to 2-year LC of 85.6% based on meta-regression. Grade 3+ toxicity was 1.8% and was mostly bowel or stomach ulcers and associated bleeds. Only 5 patients (0.5%) were reported to have developed grade 2 adrenal insufficiency, and 1 patient (0.1%) developed hypertensive crisis.

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