Radiation therapy to manage isolated relapse after chimeric antigen receptor T-cell therapy in multiple myeloma

Chimeric antigen receptor T-cell therapy (CAR-T) targeting B-cell maturation antigen (BCMA) has been approved for treatment of relapsed/refractory multiple myeloma (MM), leading to unprecedented response rates in a heavily pretreated population.[1,2] However, many patients ultimately relapse after CAR-T.[3] While there may be many theories for relapse,[4] myeloma patients who relapse after CAR-T may be treated with bispecific antibodies, repeat CAR-T, stem cell transplantation, as well as other therapies to improve survival.[5]

Here, we present two patients with multiple myeloma who had isolated sites of soft tissue plasmacytoma relapse following CAR-T. The study has been approved by the Massachusetts General Hospital Institutional Review Board and adheres to all ethical standards. Radiation therapy (RT) has historically been important for local control when MM presents as soft tissue plasmacytoma or for pain due to lytic disease as myeloma is radiosensitive, with doses of 8-30 Gy as per the International Lymphoma Radiation Oncology Group (ILROG),[6] but has not been well-studied in the CAR T-cell therapy era. These two patient cases highlight how RT can play an important cytoreductive role to quickly achieve remission in this setting.

The first patient is a 61-year-old male with stage II IgG kappa MM diagnosed ten years prior to CAR T-cell therapy. The patient began treatment with lenalidomide and dexamethasone. As the disease progressed, the patient was treated for five months with cycles of pomalidomide, ixazomib, and dexamethasone until a year prior to CAR-T administration. This systemic treatment was modified frequently, until two months prior to CAR T-cell therapy. One week prior to CAR-T, the patient's blood counts (neutrophil count ≥ $0.5x10^9$/L and platelet count ≥ $50x10^9$/L) were within normal limits. Two days prior to CAR-T, the patient was admitted to receive bridging therapy with cyclophosphamide, bortezomib, and dexamethasone. CAR-T was administered (day 0) following a protocol that utilized investigational CAR T-cell therapy targeting BCMA, with a dramatic reduction in kappa free light chains one month after treatment.

Thirty days after CAR-T, the patient was reported to be doing well, with no fevers, no lymphadenopathy, or mental status changes. Eleven months following CAR-T, the patient presented with a rapidly growing, bulky neck mass measuring 6.8 x 9.4 x 13.4 cm (Figure 1), accompanied by a sharp rise in free light chains, consistent with relapse. RT was urgently started, with 20 Gray over 5 fractions delivered to the neck mass. RT was given without bispecific antibody, and free light-chain levels reduced from 138.6 mg/L to 6.5 mg/L with RT alone. Seventeen days following RT, the patient was started on elotuzumab, lenalidomide, and dexamethasone. The elevation in free kappa light chains that was noted alongside disease progression was significantly reduced after RT with resolution of the neck mass (Figure 2). Fifteen days after RT was completed, the patient stated "90%" clinical improvement, with significant tumor regression, and no cytopenias were present. Any residual neck swelling had resolved. Mild dysphagia from RT resolved completely 70 days following treatment.

Two and a half years after CAR T-cell therapy, the patient presented with elevated free light chains again, and, two months later, a bulky right retroperitoneal mass (Figure 1) extending from the suprarenal space to the right groin and measuring 23 x 20 x 28 cm was found on a PET/CT scan. This finding was confirmed to be an isolated relapse as bone marrow biopsy prior to treatment demonstrated no morphological evidence of plasma cell neoplasm. He was initiated on elranatamab-bcmm and this disease progression was treated a month later with RT of 24 Gray over 16 fractions, with 2 fractions administered per day at a low-dose rate, to the retroperitoneal region, as the entire right kidney was within the radiation field. The patient developed fatigue and diarrhea for 5-7 days after RT, which resolved a month later. No cytopenias were demonstrated following RT. Twenty-seven days following the completion of this course, abdominal and pelvis CT scans demonstrate excellent response to RT with decrease in soft tissue density (Figure 3). Furthermore, bone marrow biopsy conducted a year following radiation treatment demonstrated no evidence of plasma cell neoplasm.

The second patient was diagnosed with lambda light chain MM 26 months prior to CAR T-cell therapy. The patient began treatment with isatuximab a month after diagnosis; however, the protocol was discontinued 12 days later due to acute renal failure. Two years prior to CAR-T, the patient had received daratumumab-RVD (lenalidomide, bortezomib, dexamethasone) systemic therapy for ten months. Thirteen months prior to CAR T-cell therapy, light chains increased, and carfilzomib (CFZ) and daratumumab treatment were implemented for seven months. Five months before CAR-T, the patient presented with a 7 cm FDG-avid anterior mediastinal mass. RT was administered to the anterior mediastinal region at 20 Gray in 10 fractions, alongside dara/CFZ/dex treatment. An extraosseous tumor was found after a month at the L4 spinal level, which was treated with RT, 20 Gray in 5 fractions. With the disease progression, the patient was

started on CyBorD, a combination of cyclophosphamide, bortezomib, and dexamethasone three months before CAR-T. Two weeks later, chemotherapy was halted for upcoming cilta-cel CAR T-cell therapy. One day prior to CAR-T cell therapy, the patient presented with mild cytopenia, with a decreasing neutrophil count, but stable hemoglobin and platelets. Cytokine release syndrome (CRS) markers showed no active inflammation, and there was no evidence of tumor lysis syndrome. Five days after apheresis, cyclophosphamide and bortezomib therapy was administered to bridge to CAR T-cell therapy. Cilta-cel was then administered.

One month after CAR-T, the PET scan showed significant decrease in disease burden. The hospital course was notable for neutropenic fever and grade 1 CRS. Cytopenia showed improvement at this time, with a neutrophil count > $1x10^9$/L. Twelve months post CAR-T, the patient relapsed with FDG avid left lateral perinephric masses present on PET/CT (Figure 1). Additionally, elevation in free light-chain levels was observed at this time (Figure 2) Prior to treatment, bone marrow biopsy confirmed the isolation of this relapse as it demonstrated no morphologic evidence of plasma cell neoplasm. The patient was started on elranatamab eight days after the mass was found. Additionally, to treat this mass, RT was administered concurrently to the left lateral

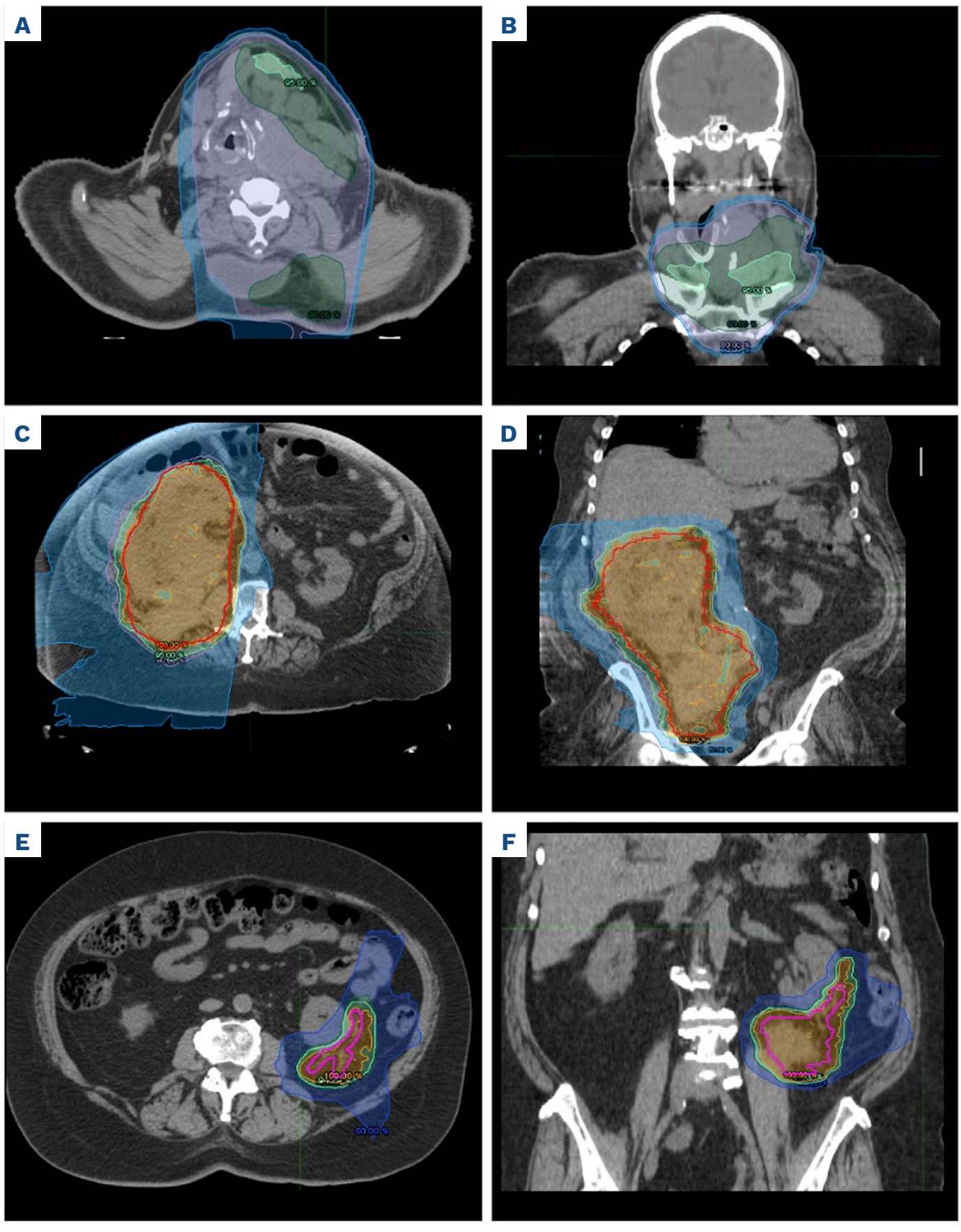

Figure 1. Radiation therapy plans. (A) Patient 1: neck plasmacytoma; axial view. (B) Patient 1: neck plasmacytoma; coronal view. (C) Patient 1: right retroperitoneal region (outlined in red); axial view. (D) Patient 1: right retroperitoneal region; coronal view. (E) Patient 2: left lateral perinephric region (outlined in pink); axial view f. (F) Patient 2: left lateral perinephric region; coronal view.

perinephric/abdominal region at 20 Gray over 10 fractions a month following relapse. The patient had excellent response on daily cone-beam CT imaging carried out during radiation treatment. At one week and one month following RT no major toxicities were observed, including but not limited to CRS, cytopenia, and infections. Mild residual nausea and fatigue associated with RT were fully resolved two months after treatment.

These cases exemplify the efficacy of RT in the case of post CAR T-cell therapy relapse in MM. It is evident from imaging as well as free light-chain data that RT provides rapid cytoreduction, alone or in combination with other therapies, without significant added toxicity. Patient 1's reduction in mass size for both the neck plasmacytoma and the retroperitoneal mass and decrease of free kappa light chains coincide well with the timeline for RT administration (Figures 1 and 2). Furthermore, Patient 2 experienced significant decrease in the perinephric mass and lambda free light chain which also corresponded to RT times (Figures 1 and 2). Regarding the RT dosing, the ILROG recommends doses of 8-30 Gy hypofractionated radiation for bony site symptom relief. For situations when the disease needs to be controlled locally, 30 Gy in 10-15 fractions, with 5 fractions each week may be used.[6] Similarly, National Comprehensive Cancer Network (NCCN) guidelines delineate symptomatic MM RT dosing to range from 20-30 Gy over the course of 5-15 fractions. Ideally, to reduce toxicity, 20-25 Gy in 8-10 fractions is preferred for these purposes, as bone marrow toxicity is a concern

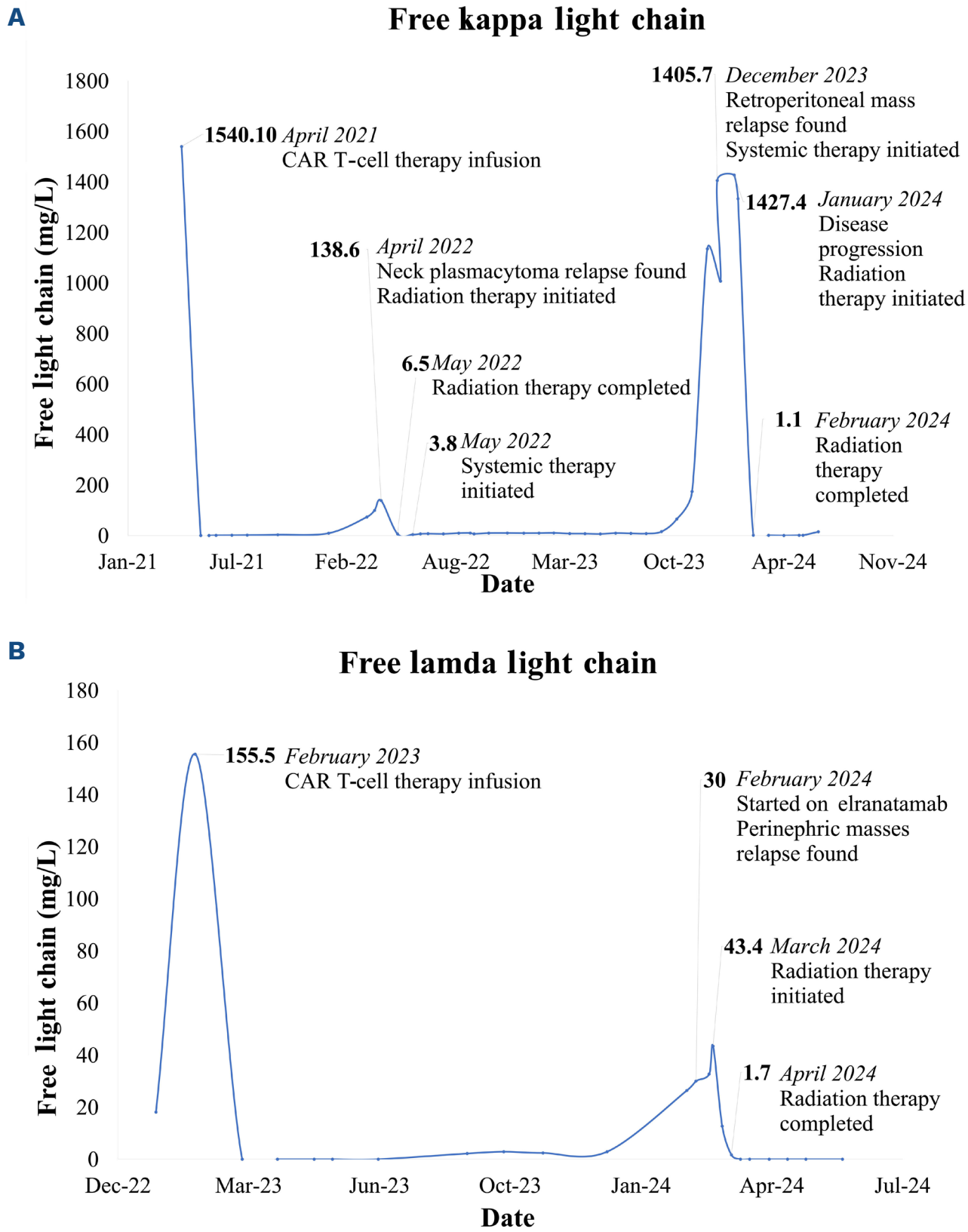

Figure 2. Serum free light-chain values. (A) Kappa free light chains: Patient 1. (B) Lambda free light chains: Patient 2.

at higher doses.[7] Optimal dosage is difficult to pinpoint, particularly with relapse after CAR-T; however, these guidelines provide a foundational framework on which to base treatment. While long-term local control is common within the field, RT is not viewed as a life-prolonging treatment for myeloma, although the cases presented here may challenge that perspective when systemic options are limited.

Through exploring these two cases, it is evident that RT can provide rapid local disease control, with reduction in free light-chain levels and improvement on PET/CT, alone or in combination with bispecific antibody therapy. This series shows that RT can remain highly effective in heavily pre-treated MM even following CAR-T cell therapy. With the treatment being administered over the course of around a week, the brevity of the treatment course allows for an expedited way to alter the disease trajectory in these patients. The efficiency and efficacy of this treatment was evident through quick patient response, and significant reduction in disease. Furthermore, RT is impressively effective at reducing large masses. The first patient presented with massive right retroperitoneal tumor spanning the suprarenal space to the groin and measuring 23 x 20 x 28 cm. Following RT, this mass showed a huge reduction, demonstrated in Figure 3.

While this series demonstrates the high efficacy of RT for these patients, there is still a risk for toxicity and radiation-induced cytopenia in patients receiving this treatment for myeloma. Recent literature determined that radiation of 10 Gy or higher to the bone marrow and a larger area of irradiation puts patients at risk of developing cytopenias.[8] Patients with MM, particularly when heavily treated, are at a higher risk due to the pre-existing hematologic vulnerability.[8] National Comprehensive Cancer Network (NCCN) guidelines confirm that systemic therapy can be given in conjunction with RT as evidence supporting toxicity is limited.[7]

Our case series highlights that RT for extramedullary relapsed MM after CAR-T is an important treatment option. Through its effectiveness, rapidity at achieving response, its ability to control large masses, and its role in reducing elevated free light chains, RT has great potential to provide urgent relief for patients with progressive isolated extramedullary relapses in MM after CAR T-cell therapy.

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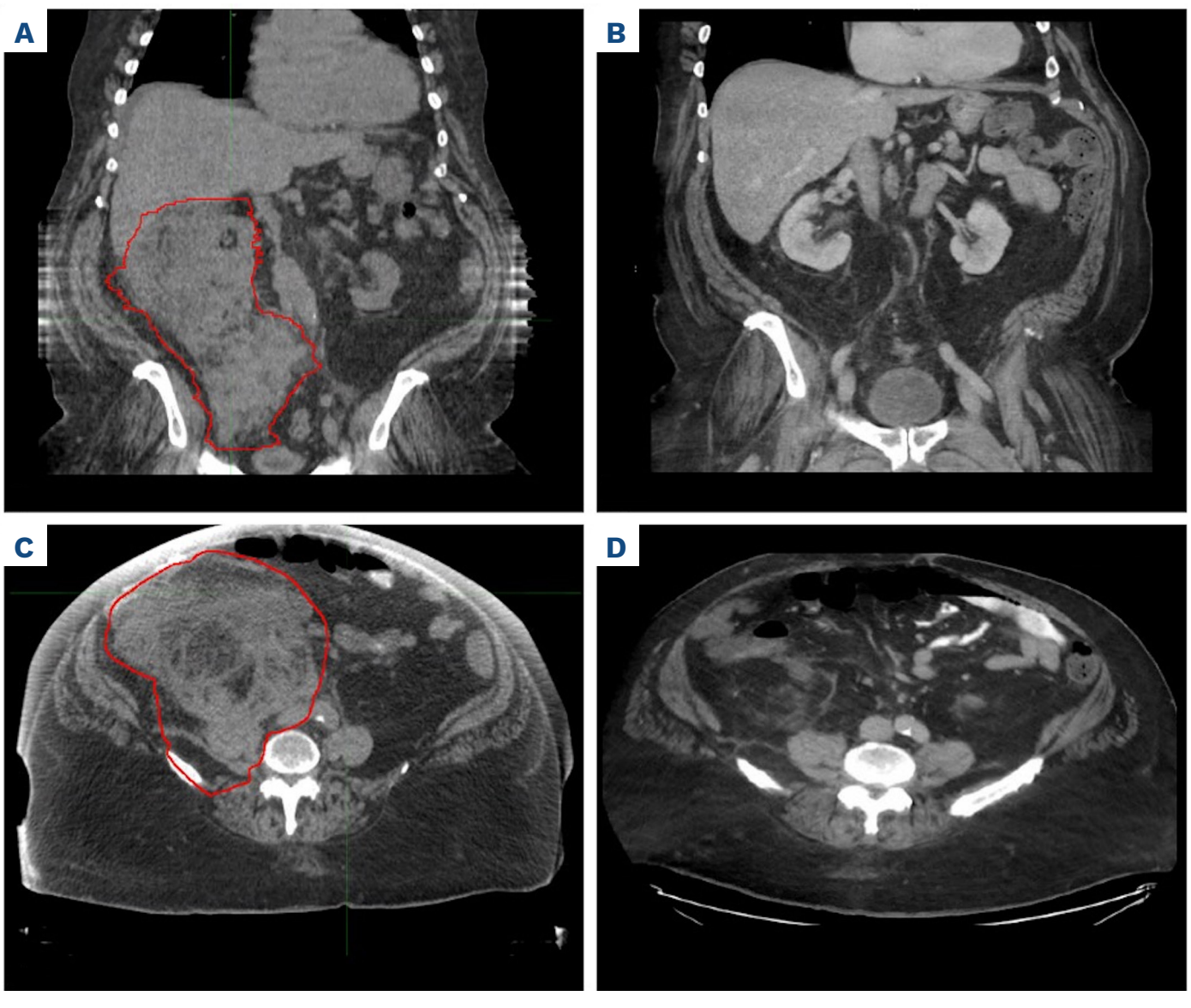

Figure 3. Patient 1 right retroperitoneal tumor reduction following radiation therapy. (A) Patient 1 coronal view prior to radiation. (B) Patient 1 coronal view 27 days after radiation. (C) Patient 1 axial view prior to radiation. (D) Patient 1 axial view 27 days after radiation.

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https://doi.org/10.3324/haematol.2025.287358

Received: January 22, 2025.
Accepted: May 28, 2025.
Early view: June 5, 2025.

Disclosures

CP reports consulting fee from Novartis and research grant from Varian. NR reports consulting fee from ER Squibb & Sons, Janssen, Pfizer, and Genzyme, and travel expenses from Celgene. All of the other authors have no conflicts of interest to disclose.

Contributions

SS was involved in data collection, and manuscript writing and revision. CP was involved in study design, project oversight, and manuscript revision. LZ and NR helped revise the manuscript.

Data-sharing statement

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent.

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