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Successful Treatment of a Large Soft Tissue Sarcoma With Irreversible Electroporation

Introduction

Irreversible electroporation (IRE) is a promising technique for the focal treatment of pathologic tissues that involves placing minimally invasive electrodes within the targeted region. A series of short, intense electric pulses are then applied to destabilize the cell membrane, presumably by creating nanopores,[1] inducing cell death in a nonthermal manner.[2] The unique therapeutic mechanism of IRE does not rely on tissue temperature changes, as with hyperthermic or cryoablative procedures.[3,4] Therefore, IRE preserves the extracellular matrix, major tissue vasculature, and other sensitive structures.[5-7] Treated regions resolve rapidly,[5] with submillimeter resolution between treated and unaffected cells,[8] and are predictable with numerical modeling.[9] Treatments promote an immune response,[5,10,11] are unaltered by blood flow, can be administered quickly (approximately 5 minutes), and can be visualized in real time.[10,12]

IRE has been studied extensively in healthy tissue,[5,6,8-10,12-13] and tumors have been treated with IRE in mice.[14-17] IRE has been attempted in humans for prostate, lung, kidney, and liver cancers.[7,18-20] Human treatments revealed negligible postablation pain and the ability to apply the pulses in proximity to vital structures.[7]

Overall, assessment of the therapeutic efficacy of IRE remains in its infancy. We hypothesize that IRE treatments can be designed and implemented to successfully treat soft tissue malignancies, including large and complex tumors, a crucial step for translation of the technology into routine clinical use. Here we report our treatment of a focal histiocytic sarcoma of the coxofemoral joint in a canine patient. Follow-up examinations demonstrated prolonged relief of cancer-associated pain, preservation of pelvic limb function, and complete tumor regression 6 months after initial treatment.

Case Study

The patient was a 7-year-old spayed female Labrador retriever with a 5-year history of degenerative coxofemoral joint disease, resulting in bilateral pelvic limb lameness. Before referral, the left pelvic limb lameness had progressed to the point of frequent non–weight-bearing lameness, refractory to medical management (Data Supplement). Examination revealed postural reaction deficits associated with sciatic neuropathy and an extensive periarticular mass involving the left coxofemoral and proximal thigh. Biopsies of the mass were cytomorphologically and immunohistochemically consistent with histiocytic sarcoma (positive immunoreactvity to CD1, CD11c, CD18, and MHC II). No evidence of metastatic disease was detected on full body radiographic and computed tomography (CT) examinations. Significant bilateral coxofemoral degenerative joint disease made the patient a poor candidate for current standard-of-care hemipelvectomy with hindlimb amputation.

Planning. CT scans of the pelvis and hindlimbs visualized the targeted region, which partially surrounded the femur and was adjacent to the sciatic nerve and femoral arteries (Figs 1A to 1C; black arrows, arteries; white arrows, sciatic nerve). Treatment planning was performed using previously described techniques,[21,22] in which a three-dimensional preoperative tumor volume of 136 mL (Fig 1D) was determined.[21,22] Two electrode styles were examined—1-mm-diameter needle dual probes and a single 1.65-mm-diameter probe—dimensions smaller than those of radiofrequency and cryoablation probes.[3,4] Predicted treatment regions were arranged to palliate the pain and lameness while ensuring functional limb sparing through preservation of the adjacent sciatic nerve and femoral artery, resulting in a three-stage electrode insertion (Fig 1E; representative treatment regions shown in Fig 1F).

Treatment. General anesthesia was induced with propofol and maintained with isoflurane. A preservative-free morphine and bupivacaine epidural was performed, and atracurium was administered intravenously. The electrodes were then inserted with CT guidance according to the treatment plan (Figs 1G to 1I). Pulses were applied according to Table 1 using the Nanoknife (AngioDynamics, Queensbury, NY). After pulsing at the deepest insertion, the electrodes were withdrawn before administration of the next pulses to prevent overlap of IRE regions, reducing insertions and preventing potential reseeding along needle tracks. Intraoperative temperature monitoring at the electrode showed a maximum change of 2.43°C, with temperatures returning to baseline within 3 minutes.

Clinical results. The left sciatic nerve was electrophysiologically evaluated before and immediately after IRE therapy using standard procedures with a commercial electrodiagnostic system (Nicolet Viking IV; Nicolet Instruments, Madison, WI). These revealed small decreases in the amplitudes of the distal compound muscle action potentials compared with pre-IRE values, suggestive of mild conduction block (Figs 2A, 2B; Table 2). The patient was hospitalized for 24 hours and received oxymorphone. The acute post-IRE electrophysiologic changes were subclinical; the degree of lameness and sciatic nerve dysfunction observed 24 hours after IRE remained unchanged from pretreatment. Biopsies taken 24 hours after IRE revealed coagulative necrosis of the tumor, and the dog was discharged to continue therapy with deracoxib and tramadol. At a recheck 8 days after IRE, the owner reported improvement such that the dog no longer had episodes of non–weight-bearing lameness, and tramadol was discontinued 4 days after IRE therapy. Day-8 CT showed tumor volume of 65 mL, a 52% reduction versus pre-IRE treatment, although intrapelvic lymphadenopathy and focus of tumor in the proximal region of the femur outside of the targeted IRE treatment area were visualized. Metastases were cytologically confirmed as the cause of the lymphadenopathy. Thus, a chemotherapeutic regimen of 1-(2-chloroethyl)-3-cyclohexyl-*l*-nitrosurea (CCNU; 65 mg/m^2 orally every 21 days) was prescribed.

The temporal relationships of treatments on gross measurable disease are summarized in Figure 3 (US, ultrasound). By 2 weeks after

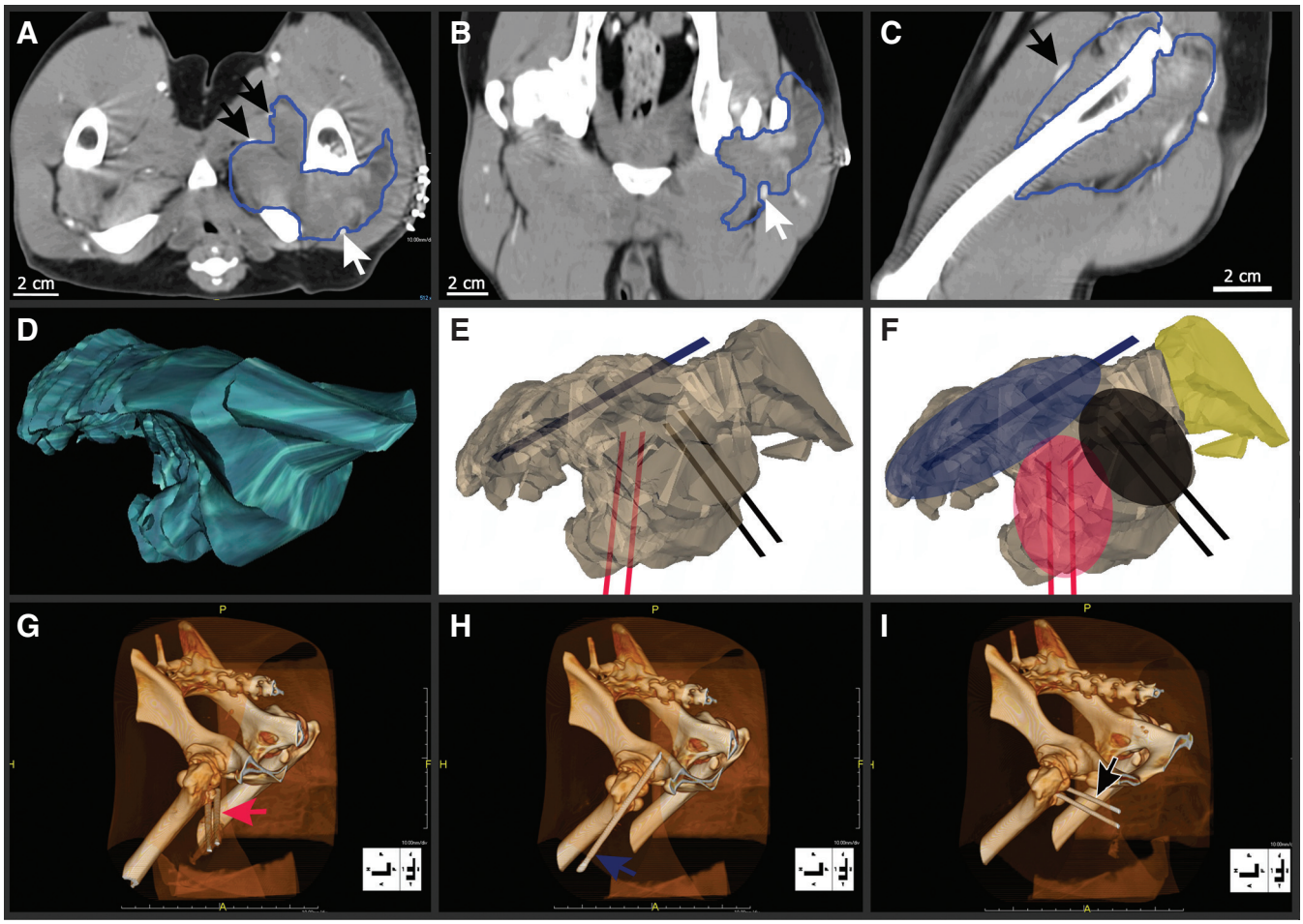

Fig 1.

IRE, the lameness had improved such that the dog was capable of daily activities, including controlled leash walks and swimming, with gait deficit in the left pelvic limb indistinguishable from that of the right. The left sciatic nerve was electrophysiologically re-evaluated, with results having returned to pretreatment values (Table 2). All prescribed analgesic medications were discontinued by 2 months after IRE. By 13 weeks post IRE, the entire originally targeted tumor volume and lymph node metastases had been completely eliminated.

Re-treatment. A 4-month recheck visualized a new 36-mL focus of tumor on CT and ultrasound examinations in a region outside the previous IRE treatment field in the medial aspect of the left coxofemoral region (Figs 4A to 4C; arrows, box), suggesting development of

Table 1. Physical and Pulse Parameters

Pulse Application Set	Insertion	Electrode Style (probe)	Separation (cm)	Depth (cm)	Voltage (V)	Repetition Rate (pulses per minute)
1/1	1	Dual	1	6.5	1,000	90
1/2	1	Dual	1	5	1,250	90
1/3	2	Single	0.8	11	1,000	90
1/4	2	Single	0.8	8	1,200	90
1/5	2	Single	0.8	6	800	90
1/6	3	Dual	1	1.4	1,500	90
1/7	3	Dual	1	0.9	1,000	90
2/1	4	Dual	1.5	4.1	1,150	ECG
2/2	5	Dual	1.5	4.1	1,150	ECG

NOTE. All sets of 80 pulses had pulse lengths of 100 μs except treatment 2/2, which had 70 μs.

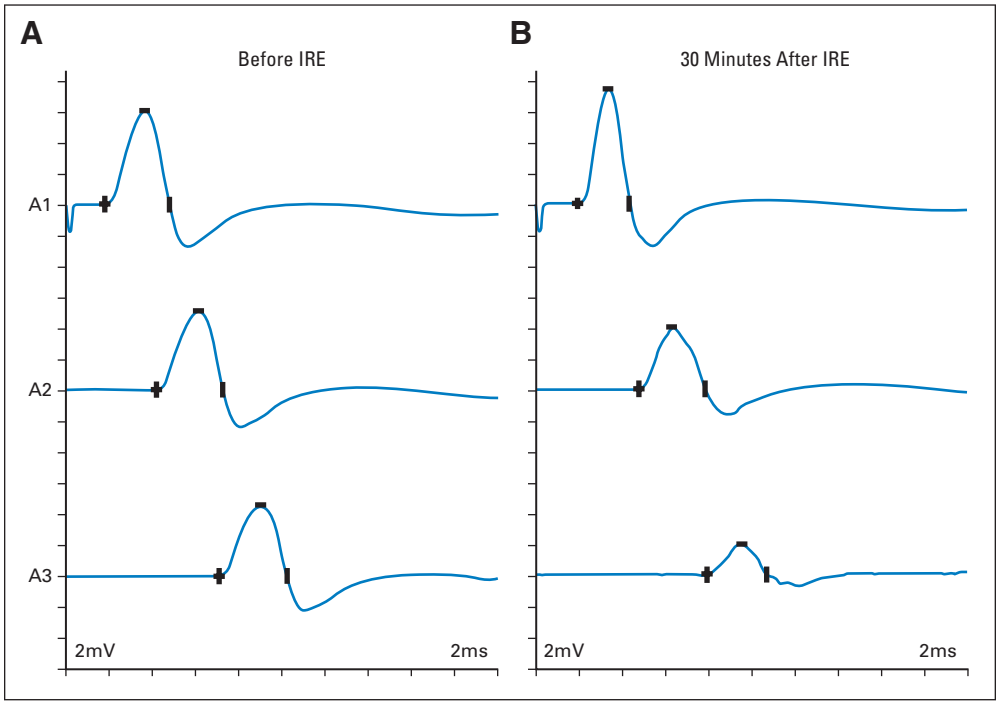

Fig 2.

chemoresistance to CCNU. A second IRE session with a parallel three-needle electrode array was selected to treat this focal relapse. Ultrasound guidance facilitated electrode placement (Fig 4D), with the center energized (2.5-cm exposure length) and one side grounded at a time (1.5-cm exposure), for a total of two pulse sets (Table 1). Pulses were synchronized to 500 μs after the *R*-peak wave of the patient's cardiac rhythm.

Both IRE treatments resulted in progressive coagulative tumor necrosis in the periods of 24 to 48 hours post therapy (Figs 5A to 5F; hematoxylin and eosin stain), and the majority of skeletal muscle at the margin of the tumor remained viable (Figs 5A to 5C). In addition, the IRE resulted in marked influx of mixed inflammatory infiltrate into the treatment region, which was composed of neutrophils, macrophages, and primarily CD3+ lymphocytes (Figs 5G to 5I; CD3 with fast red counterstain).

Volumetric tumor regression occurred for several weeks after IRE (Fig 3), as necrotic tissue was resorbed by the immune system and local tissue healing and remodeling occurred. At the 6-month recheck, the patient was in complete remission according to clinical and CT examinations (Data Supplement). The dog displayed mild, bilaterally symmetric pelvic limb lameness consistent with the degenerative joint disease but was capable of daily low-impact exercise (ie, walking, swimming) without exacerbation of lameness and was receiving no adjunctive analgesic. There was no evidence of the tumor on CT scan (Figs 4F to 4G), which was also confirmed by biopsy of the region.

Table 2. Motor Conduction Study of Left Sciatic Nerve

Evaluation	Left Sciatic Tibial Nerve	Latency (ms)	Amplitude (mV)	Segment	Latency Difference (ms)	Distance (mm)	Conduction Velocity (m/s)
Before IRE	Hock (A1)	1.8	6.1	Interosseous muscle—hock	1.8	30	17
	Stifle (A2)	4.2	5.1	Hock—stifle	2.4	150	63
	Hip (A3)	7.1	4.6	Stifle—hip	2.9	185	64
				Hock—hip	5.3	335	63
30 minutes after IRE	Hock (A1)	1.9	7.6	Interosseous muscle—hock	1.9	30	16
	Stifle (A2)	4.6	4.1	Hock—stifle	2.7	150	56
	Hip (A3)	8.0	2.2	Stifle—hip	3.4	185	54
				Hock—hip	6.1	335	55
2 weeks after IRE	Hock (A1)	1.7	7.4	Interosseous muscle—hock	1.7	30	18
	Stifle (A2)	4.0	5.3	Hock—stifle	2.3	150	65
	Hip (A3)	6.9	4.8	Stifle—hip	2.9	185	64
				Hock—hip	5.2	335	64

Abbreviation: IRE, irreversible electroporation.

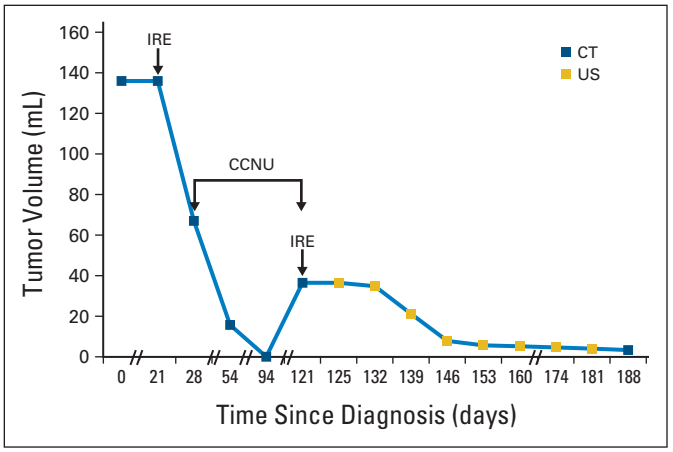

Fig 3.

Discussion

Our report provides novel and encouraging results regarding the future role of IRE in clinical oncology. As the scope of IRE therapy expands to increasingly diverse clinical settings, it is vital to be able to use IRE in settings in which neighboring structures make surgical resection and other focal techniques impractical or dangerous. The original tumor was greater than 136 mL in volume and located in a heterogeneous setting that encompassed bone, muscle, major arteries, and the sciatic nerve.

Canine histiocytic sarcoma is a biologically aggressive neoplasm associated with a grave prognosis, with studies reporting median survival between 3 and 6 months with treatment.[23,24] Given its biologic behavior, we believe the therapeutic clinical outcome we report is excellent. We were able to achieve complete remission 6 months after diagnosis with multimodality IRE and chemotherapy, while improving quality of life for the patient and owner. Additionally, we completely ablated relapsed and suspected chemoresistant tumor using IRE alone with minimal collateral damage to healthy tissues. This demonstrates the potential of IRE as a primary therapy or when faced with neoplasms refractory to other therapy. Our real-time in vivo temperature monitoring data illustrate that the therapeutic effect occurs via nonthermal mechanisms.[2,15,25] The biopsies from this patient demonstrated sparing of the muscle at the tumor margins. Although IRE can ablate tumors independent of an associated immune response,[14] we observed significant infiltration of T-lymphocytes into the tumor.

This investigation used IRE to achieve complete remission and improved quality of life in a canine patient with a large and complex tumor in a heterogeneous environment. An initial treatment resulted in improved clinical signs of cancer-associated pain without adverse effects and allowed functional limb sparing. A strong tumor response to IRE with adjuvant chemotherapy was later observed. After development of chemoresistance, new tumor growth was treated with a second application of IRE, which resulted in complete remission 6 months after initial treatment. Postoperative biopsies showed complete tumor necrosis with sparing of adjacent muscle. These findings demonstrate the feasibility and efficacy of IRE as an attractive, minimally invasive, primary ablative therapy for the treatment of soft tissue malignancies.

Robert E. Neal II
Virginia Tech–Wake Forest School of Biomedical Engineering and Sciences, Virginia Tech, Blacksburg, VA

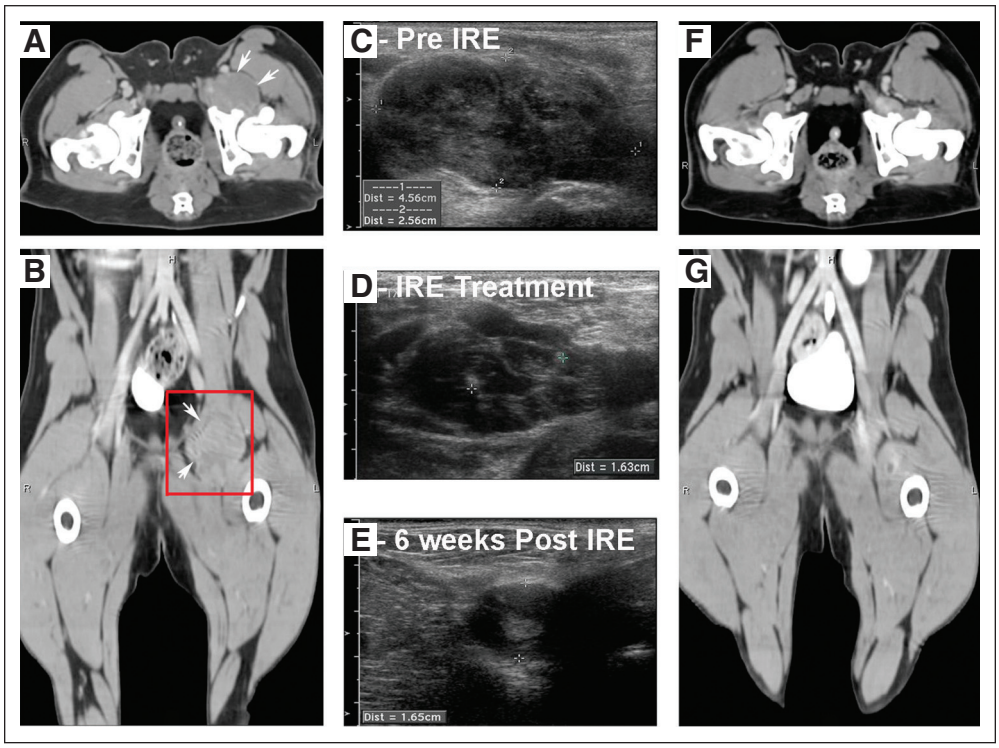

Fig 4.

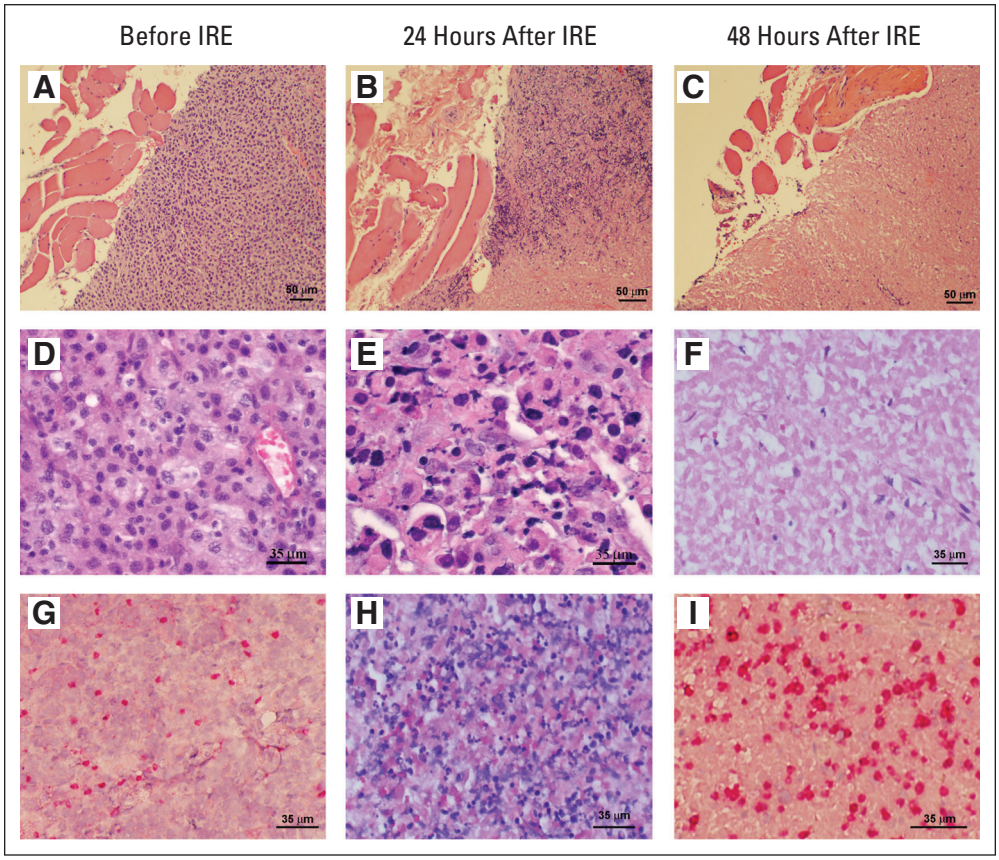

Fig 5.

John H. Rossmeisl Jr
Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA

Paulo A. Garcia
Virginia Tech–Wake Forest School of Biomedical Engineering and Sciences, Virginia Tech, Blacksburg, VA

Otto I. Lanz and Natalia Henao-Guerrero
Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA

Rafael V. Davalos
Virginia Tech–Wake Forest School of Biomedical Engineering and Sciences, Virginia Tech, Blacksburg, VA

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