Undersea & Hyperbaric Medicine, Vol. 22, No. 4, 1995

Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases

J. J. FELDMEIER, R. D. HEIMBACH, D. A. DAVOLT, W. S. COURT, B. J. STEGMANN, and P, J. Sheffield

Department of Radiation Oncology, Grace Hospital and Wayne State University, Detroit, Michigan; and Department of Hyperbaric Medicine Southwest Texas Methodist Hospital and the Nix Hospital, San Antonio, Texas

Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases. Undersea Hyperbaric Med 1995; 22(4):383–393.—Since 1979, 23 cases of radiation-induced chest wall necrosis have been treated in the Hyperbaric Medicine Departments of Southwest Texas Methodist Hospital and the Nix Hospital, San Antonio, Texas. Eight cases involved soft tissue only. Six of eight (75%) patients with soft tissue involvement healed without requiring surgical debridement, although four patients (50%) did have flaps or grafts. Fifteen patients had bony and soft tissue necrosis. Eight of these patients (53%) resolved with adjunctive hyperbaric oxygen (HBO), but all required aggressive surgical debridement including skeletal resection. Four (27%) had reconstructive flaps as well. Six patients (40%) with bony necrosis who had either no or incomplete debridement failed to heal. Three patients (13%) (two soft tissue and one bony) were found to have residual tumor during HBO and were discontinued from treatment. HBO is an effective adjunctive therapy for soft tissue chest-wall, radiation-induced necrosis, but must be coupled with appropriate debridement to include surgical removal of all necrotic bone to ensure a successful outcome of bony plus soft tissue necrosis.

hyperbaric oxygen, radiation necrosis, breast cancer:

It is estimated that one of every eight women alive today in the United States will eventually develop breast cancer (1). Conservative therapy involving lumpectomy, axillary dissection, and breast irradiation is becoming an ever more frequent option for early breast cancer (2). This conservative procedure results in control rates that are virtually identical to modified radical mastectomy and permits the patient to keep her breast, thus reducing psychological and physical trauma (3). Moreover, radiation therapy is often indicated as a adjuvant to mastectomy when certain poor prognostic factors are present, including large tumors, multiple metastatic axillary lymph nodes, positive margins of resection, or pectoralis muscle involvement (4).

When radiation therapy is given in either of the above settings, the radiation fields are generous, usually encompassing one-half of the anterior chest wall and sometimes expanded to include the axilla and/or supraclavicular fossa (5). Radiation doses are moderate to high with large volumes of tissue treated to 5,000 cGy and areas of gross tumor involvement treated as high as 7,000 cGy (6).

The chest wall is also included in the radiation portal of tumors involving other organs anatomically located near or below the chest wall. In most of these cases, such as lung cancer, esophageal cancer, or mediastinal lymphoma, the skin-sparing effects of high-energy radiation can be utilized to reduce the radiation dose to the skin and subcutaneous tissues. In doing so the likelihood of skin and subcutaneous complications is reduced.

Therefore, we find today a large population of women who have had radiation to their breasts and/or chest walls and are potentially at risk for late radiation damage. We also find a smaller group of patients at risk due to treatment for tumors other than breast cancer. Fortunately, serious sequelae of breast and/or chest wall radiation are relatively rare. In 189 patients treated with breast conservation, Danoff et al. (7) reported arm edema in 7%, symptomatic radiation pneumonitis in 1%, rib fractures in 1%, pericarditis in 1%, and pleural effusion in 1%. In a review of 146 patients, Kantarowitz and associates (8) reported moderate complications in 6.8% of patients, consisting mostly of edema of the breast or arm or pain in the shoulder, arm, chest wall, or breast. In a report of 108 patients treated with conservation of the breast, Schmidt-Ulrich and associates (9) reported moderate edema, fibrosis, and discomfort in 9% of patients and severe sequelae in about 2%. Montague (10), in reporting the MD Anderson Hospital experience of radiating advanced breast cancers, detected a 20% incidence of severe subcutaneous fibrosis, 5–10% incidence of rib fractures, and an even lower incidence of skin necrosis and ulceration (10).

In cases of minimal necrosis, conservative management with the treatment of secondary infection and analgesia for symptomatic relief may be adequate. When extensive radiation necrosis of the chest wall does occur it is a difficult therapeutic challenge. The recommended surgical management of serious chest wall necrosis requires aggressive resection of all necrotic material and reconstruction utilizing either omental flaps or myocutaneous flaps which preferably have their origin outside the radiation field (11–13).

Arnold and Pairolero (11) have reported their results in the management of 50 patients with radiation-related injuries of the chest wall. In this series, 23 patients had soft tissue ulcers, 7 had infected sternal wounds; and 20 had recurrent cancers. All 50 of these patients underwent chest wall resection. Three quarters of these required "skeletal" resections. Patients underwent an average of 2.6 surgeries with a range of 1 to 8. Thirty-six patients (72%) were alive with a healed chest wall at an average 28-mo. follow-up, and one operative death occurred. The authors report that the other 14 patients died, most from recurrent tumor.

The success of HBO as an adjuvant for mandibular necrosis has encouraged the HBO community to apply this modality in radiation necrosis of other anatomic sites. In 1976, Hart and Mainous (14) published their results in the use of HBO as treatment for radiation necrosis of many sites including chest wall, pelvis, nervous system, and larynx. These results were positive for the most part. However, only a few cases were reported for each site. Other reports have discussed the results of HBO in the treatment of radiation-induced necrosis of the larynx (15,16) and radiation-induced hemorrhagic cystitis (17–19).

The pathophysiology of delayed radiation necrosis includes advanced arteriocapillary fibrosis (20). In areas of ulceration, the vascular and connective tissues provide poor support for re-epithelialization. Heimbach (21) has previously discussed the rationale for the use of HBO in delayed radiation injuries. In hypoxic and ischemic tissues, HBO enhances the oxygenation of irradiated tissues and stimulates neovascularization. Marx and Ames (22) have reported their success in using HBO as an adjunct to mandibular reconstruction of irradiated patients, and have demonstrated evidence of neovascularization in the recipient bed of mandibular grafts. Marx and associates (23) have also demonstrated a dose-response curve for the neovascularization of tissues according to dose of oxygenation.

This paper discusses the experience of a single physician group in applying HBO as an adjuvant therapy for radiation-induced necrosis of the chest wall. The Radiation Therapy Oncology Group (RTOG) and the European Organization for the Research and Treatment of Cancer (EORTC) have collaborated to establish a grading system to evaluate the severity of late radiation complications (24). Table 1 summarizes this scoring system for skin and bone injuries. This scoring system was applied to the injuries reported in this paper.

MATERIAL AND METHODS

This report is a retrospective review of 23 cases of chest wall radiation necrosis referred to our institutions since 1980; 1 of these patients was referred on two separate occasions for chest wall necrosis involving two distinct sites. One patient (number 7 from Table 2B) had two courses of HBO consisting of 127 HBO treatments before referral to our center. These prior treatments had been given 7 yr earlier.

Eight patients were treated for soft tissue radiation damage and 15 had both bony and soft tissue necrosis. Of the eight patients with soft tissue radiation damage, six had grade 4 and two had grade 3 injuries. All patients with bone-plus-soft-tissue necrosis had grade 4 injuries, with necrotic exposed bone. For soft tissue injury, the median time of onset after radiation was 15 mo. (range immediately post-treatment to 7 yr after radiation). For bony radiation necrosis the median time of onset after completion of irradiation was 16 yr (range from 6 mo. to 27 yr after radiation therapy). For soft tissue necrosis, patients were more typically referred for HBO sooner, with a median time between diagnosis and referral of 2 mo. (range immediately to 23 yr after diagnosis). For bony radiation necrosis the median time between diagnosis and referral for HBO was 18 mo. (range immediately to 32 yr).

Table 1: Late Radiation Morbidity Scoring

Organ	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SKIN	slight atrophy, pigmentation change, some hair loss	patchy atrophy, moderate telangiectasia, total hair loss	marked atrophy, gross telangiectasia	ulceration	patient death
BONE	reduced bone density	moderate pain or tenderness, growth retardation, irregular bone sclerosis	severe pain or tenderness, complete arrest of bone growth dense bone sclerosis	necrosis	patient death

Other pre-treatment patient characteristics, including the grade of the injury, are shown in Tables 2A and 3B. The actual radiation records were not available in many cases because the time interval after radiation had been so long. Therefore, doses were estimated from standard radiation therapy guidelines. All patients were treated at 2.4 atm abs for 90 min of 100% oxygen in a multiplace chamber and were always accompanied by a medical attendant. Fastidious daily wound care was also considered an essential portion of these patients' management. Wound care was tailored to the individual case. Typically, after removal of the dressing, the outer edge of the wound was cleansed with a Hibiclens sponge. The wound was then irrigated with normal saline with high pressure irrigation. Areas of frank necrosis were sharply debrided as tolerated by the patient, using scalpel, scissors, or curette. The wound was then typically dressed with either fine mesh or coarse gauze soaked in 0.5% boric acid. This "wet-to-dry" technique was designed to provide additional debridement at the time of the next dressing. Coarse gauze was usually used for large ulcers and for those with considerable debris at the base of the ulcer. A protective dressing using additional dry gauze fluffs and/or abdominal dressing pads was generally taped in place.

RESULTS

Outcome of therapy for all 23 patients is shown in Tables 3A and 3B. For soft-tissue-only necrosis, two patients were found to have recurrent cancer and were discontinued after seven HBO treatments each. The remaining six patients (with seven treatment sites) had a successful outcome of therapy without surgical debridement. Four patients did have split thickness skin grafts and/or myocutaneous flaps. One patient had resolution of her ulcerative necrosis after only eight treatments. The average number of surgeries in this group (not including those with recurrent cancers and counting patient number 1 twice) was 0.57 surgeries per patient.

The results of therapy for patients with bone and soft tissue necrosis are given in Table 3B. Ten patients had involvement primarily of ribs, and the remaining five had the sternum as the primary site of bony necrosis. Eight of the 15 patients had a successful resolution of their radiation necrosis. All of these patients had aggressive debridement with removal of all necrotic bone. Five of these eight patients also had myocutaneous flaps to close the defect that resulted due to the underlying necrosis and surgical debridement.

The remaining seven patients failed to heal. Four of these patients had no surgical debridement. Two other patients had conservative debridement and failed to heal (numbers 13 and 15). Both of these patients were left with unresected necrotic sterna. Patient number 7 failed to heal after extensive debridements, myocutaneous flaps, and in spite of a total of 241 HBO treatments. It should be noted that this patient had been treated for sarcoma with a higher radiation dose, and even after multiple surgical debridements had residual necrotic bone when HBO therapy was discontinued. One patient in the bone-and soft-tissue group was found to have recurrent tumor after 25 treatments and was discontinued from HBO after some improvement. The average number of surgeries in this group (excluding the patient with recurrence) was 1.29. The median number of HBO sessions for those patients successfully treated was 25 in the soft-tissue-only group and 36 in the bone-plus-soft-tissue group.

DISCUSSION

When only soft tissue is involved, HBO coupled with conservative non-surgical debridement was highly effective. All patients in this group without recurrent cancer had resolu-

Table 2A: Pre-Treatment Characteristics (soft tissue only)

Patient	Age	Sex	Cancer Diagnosis	Radiation Dose, cGy	Time from Radiation to Injury	Grade of Radiation Injury	Time from Radiation Injury to HBO Referral
1	43	F	breast	6,000[a]	5 yr	4 (ulcer)	7 mo
2	67	F	breast	4,800 (pre-op)	immediately	4 (ulcer)	3 mo
3	64	F	breast	5,000 (pre-op)	10 mo	4 (ulcer)	immediately
4	71	M	prostate	3,900	3 mo	4 (ulcer)	1 mo
5	49	F	breast	6,000[a]	7 yr	3 (extensive telangiectasia)	3 mo
6	67	F	breast	5,000	1 yr	4 (ulcer)	23 yr
7	30	F	breast	5,000	18 mo	4 (ulcer)	1 mo
8	51	F	breast	6,000	20 mo	3 (extensive telangiectasia)	2 wk

[a]Estimated dose (dose based on standard radiotherapy guidelines).

Table 2B: Pre-Treatment Characteristics (bone and soft tissue)

Patient	Age	Sex	Cancer Diagnosis	Radiation Dose, cGy	Time from Radiation to Injury	Grade of Radiation Injury	Time from Injury to HBO Referral
1	78	F	breast	6,000	17 yr	4	2 mo
2	63	F	breast	6,000	11 yr	4	2 mo
3	40	F	breast	5,000–6,000[a]	20 yr	4	6 mo
4	58	F	breast	5,000–6,000[a]	1 yr	4	4 yr
5	52	F	breast	5,000–6,000[a]	4 yr	4	6 mo
6	68	F	breast	5,000–6,000[a]	20 yr	4	3 yr
7[b]	66	M	sarcoma	7,000[a]	6 mo	4	1 yr, 7 mo
8	57	F	breast	5,000–6,000[a]	6 mo	4	4 yr
9	65	F	breast	5,000–6,000[a]	27 yr	4	immediately
10	66	F	breast	7,000	1 yr	4	11 mo
11	80	F	breast	5,000–6,000[a]	20 yr	4	4 mo
12	53	F	breast	5,000–6,000[a]	5 yr	4	7 mo
13	49	F	breast	5,000–6,000[a]	25 yr	4	24 yr
14	70	F	breast	5,000–6,000[a]	1 yr	4	32 yr
15	37	F	breast	5,000–6,000[a]	15 yr	4	18 mo

[a]Estimated dose (dose based on standard radiotherapy guidelines); [b]patient had also had 127 HBO treatments 7 yr earlier at a different center.

Table 3A: Results of Treatment—Soft Tissue Only

Patient	Number of HBO Treatments	Number of Surgical Interventions	Outcome
1	17	1	healed
1 second site	8	0	healed
2	20	0	healed
3	28	1 split thickness skin graft	healed
4	32	1 myocutaneous flap with skin graft	healed
5	33	1 myocutaneous flap	healed
6	7	0	found to have recurrent cancer and D/Ced
7	7	0	found to have recurrent cancer and D/Ced
8	8	0	healed

Table 3B: Results of Treatment—Bone and Soft Tissue

Patient	Bones Primarily Involved	Number of HBO Treatments	Number of Surgical Interventions	Result
1	ribs	65 (3 courses)	2 debridements and flap	healed
2	ribs	33	1 debridement and flap	healed
3	ribs	30	0 (at surgeon's option)	failed to heal
4	ribs	53	0 (at surgeon's option)	failed to heal
5	ribs	3	0 (at surgeon's option)	failed to heal
6	ribs	49	1 debridement and flap	healed
7	ribs	114 (4 courses)	3 debridements flaps and grafts but with residual necrotic bone	failed to heal
8	ribs	87 (3 courses)	2 debridements	healed
9	ribs	26	2 debridements and flap	healed
10	ribs	25	0 discontinued when recurrent tumor demonstrated	failed to heal, recurrent tumor
11	sternum	9	1 debridement	healed
12	sternum	39	1 debridement	healed
13	sternum	46 pre and post (2 courses)	1 conservative debridement; needed sternectomy	failed to heal
14	sternum	30	2 sternectomy and flap	healed
15	sternum	63 (3 courses)	2 conservative debridements; refused sternectomy	failed to heal

tion of their necrosis with adjunctive HBO. Aggressive daily wound care in this troublesome wound was an important part of patient management.

Marx (20) has shown the need to remove all necrotic bone in mandibular radiation necrosis even when this removal requires a discontinuity procedure or hemi-mandibulectomy. Likewise, our review of chest wall necrosis strongly suggests that aggressive debridement of all necrotic bone is essential to successful resolution of bony necrosis of the chest wall. Such resections may require the removal of substantial volumes of tissue and may even require sternectomy or removal of several ribs in some instances. Just as in mandibular necrosis, even prolonged courses of HBO will not be effective unless all necrotic bone is removed.

Only 8 of 14 patients with bone-plus-soft-tissue necrosis (57%) (excluding the patient with recurrent cancer) had resolution of their radiation injury. Of the six patients who failed to heal, three had no surgical intervention, two had inadequate debridement (both had frankly necrotic sterna), and one had multiple aggressive debridements (including skeletal resections) but was left with necrotic bone even after these multiple procedures.

We might ask whether HBO is really efficacious in this situation. Since this is not a controlled study, we must compare our results to other published series. Only a few papers discuss the treatment of radiation necrosis of the chest wall (11–13). These papers are from the surgical literature and consistently recommend radical resection of all necrotic material from the chest wall, usually coupled with myocutaneous flaps or omental transpositions and sometimes with Prolene or Marlex mesh to close the resultant defect.

The most specific and quantitative of these in terms of results and methods is the previously cited paper by Arnold and Pairolero (11). In this series all patients had chest wall resections. An average of 2.6 surgeries per patient was necessary and as many as eight surgeries were required to achieve success. Overall, their success rate was 72%, but this group of patients included some with recurrent cancer as well as soft tissue or bony radiation necrosis. The authors do not distinguish between type of patient injury and number of surgeries required to achieve closure. In our report, including those patients with soft tissue or soft-tissue-plus-bony necrosis (but excluding patients with recurrent cancers) an average of 1.1 surgeries per patient were required to achieve a successful resolution of the necrosis and a healed wound. The success rate was 100% in those who had debridement of all necrotic bone and who did not have recurrent tumors.

This report is a retrospective study, and the 23 patients included came from 15 different referring physicians. Each referring physician had a different experience level and a differing willingness to aggressively address these wounds surgically. In some cases the surgeon was not willing to resect large portions of the chest wall. In other cases, the patient refused aggressive debridement. All patients included in the previously cited surgical reports were willing to undergo radical resection and reconstruction.

Four of our patients (one soft tissue and three bone-plus-soft-tissue necrosis) underwent more than one course of HBO. This split-course HBO therapy generally occurred when the patient or the referring surgeon requested an interruption in treatment. Often this break would occur at a time when the patient was being considered for a surgical debridement or after a prolonged course of treatment when the patient had plateaued in terms of response. A break at this time was indicated for logistic reasons or for the patient's emotional health. Many of the patients were from areas well outside of San Antonio and they wished to return home for their comfort or to address personal business.

Based on our experiences, both positive and negative, and based on our understanding of the mechanisms of HBO as well as the accepted principles of Marx and Ames (23) in applying HBO to mandibular osteoradionecrosis, we recommend the algorithms depicted in Figs. 1 and 2 for HBO in chest wall necrosis.

This report suffers from the usual shortcomings of retrospective reviews. Comparisons with other published studies can only be made with the greatest caution. However, our results suggest that HBO with no or conservative surgical intervention can be highly suc-

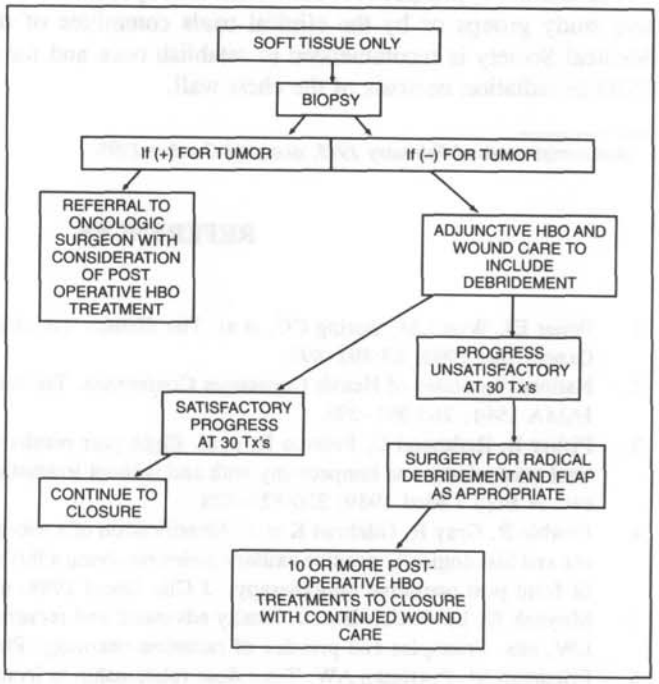

FIG. 1—Management algorithm for soft tissue injury.

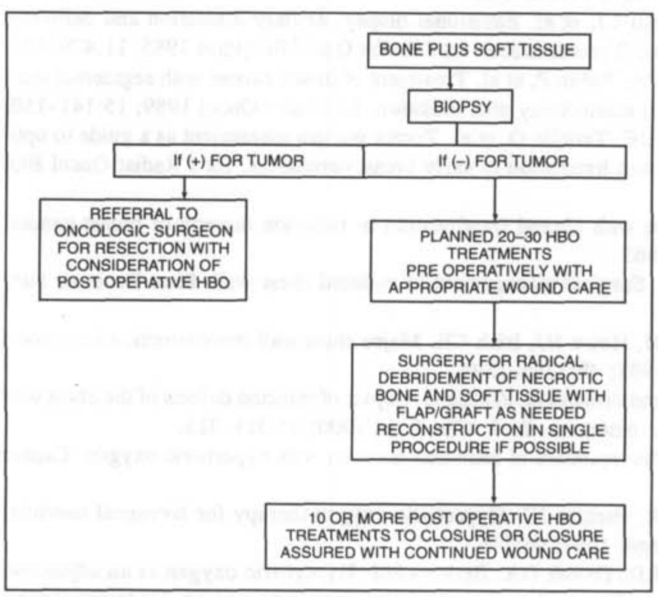

FIG. 2—Management algorithm for bone-plus-soft-tissue injury.

cessful in the treatment of soft tissue necrosis of the chest wall. When bone is involved by necrosis, HBO must be combined with aggressive surgical intervention to extirpate all necrotic bone. Even in this setting, HBO seems to have a role in reducing the number of surgeries and therefore the number of in-patient days and the inherent risk of surgical complications required to achieve successful wound closure.

A randomized, prospective, controlled trial sponsored by one of the oncologic cooperative study groups or by the clinical trials committee of the Undersea and Hyperbaric Medical Society is recommended to establish once and for all the efficacy of adjunctive HBO in radiation necrosis of the chest wall.

Manuscript received February 1995; accepted October 1995.

REFERENCES

1. Feuer EJ, Wun LM, Boring CC, et al. The lifetime risk of developing breast cancer. J Natl Cancer Inst 1993; 85:892–897.
2. National Institutes of Health Consensus Conference. Treatment of early stage breast cancer. JAMA 1991; 265:391–395.
3. Fisher B, Redmond C, Poisson R, et al. Eight year results of a randomized trial comparing total mastectomy and lumpectomy with and without irradiation in the treatment of breast cancer. N Engl J Med 1989; 320:822–828
4. Fowble B, Gray R, Gilchrist K et al. Identification of a sub-group of patients with breast cancer and histologically positive axillary nodes receiving adjuvant chemotherapy who may benefit from post operative radiotherapy. J Clin Oncol 1988; 6:1107–1117.
5. Moynak D, Levitt SH. Breast: locally advanced and recurrent tumors. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. Philadelphia: JB Lippincott, 1992.
6. Friedman M, Pearlman AW. Time dose relationship in irradiation of recurrent cancer of the breast. Am J Roentgenol 1955; 73:986–998.
7. Danoff BF, Pajak TF, Solin LJ, et al. Excisional biopsy, axillary dissection and definitive radiotherapy for stages I and II breast cancer. Int J Radiat Oncol Biol Phys 1985; 11:479–483.
8. Kantarowitz DA, Poulter CA, Rubin P, et al. Treatment of breast cancer with segmental mastectomy alone or segmental mastectomy plus radiation. Radiother Oncol 1989; 15:141–150.
9. Schmidt-Ulrich R, Wazer DE, Tereilla O, et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early breast carcinoma. Int J Radiat Oncol Biol Phys 1989; 17:733–738.
10. Montague ED. Experience with altered fractionation in radiation therapy of breast cancer. Radiology 1968; 90:962–965.
11. Arnold PG, Pairolero PC. Surgical management of radiated chest wall. Plast Reconstr Surg 1986; 77:605–612.
12. Larson DL, McMutrey MJ, Howe HJ, Irish CE. Major chest wall reconstruction after chest wall irradiation. Cancer 1982; 49:1286–1293.
13. Wening JV, Thomas G, Emmermann A, Zornig C. Repair of infected defects of the chest wall by transposition of greater omentum. Br J. Clin Pract 1990; 44:311–313.
14. Hart GB, Mainous EG. The treatment of radiation necrosis with hyperbaric oxygen. Cancer 1976; 37:2580–2585.
15. Ferguson BJ, Hudson WR, Farmer JC. Hyperbaric oxygen therapy for laryngeal necrosis. Ann Otol Rhinol & Laryngol 1987; 96:1–6.
16. Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ. Hyperbaric oxygen as an adjunctive treatment for severe laryngeal necrosis: a report of nine consecutive cases. Undersea Hyperbaric Med 1993; 20:329–335.
17. Weiss JP, Borland FP, Mori H, et al..Treatment of radiation induced cystitis with hyperbaric oxygen. J Urol 1985; 134:352–354.
18. Shoenrock GJ, Cianci P. Treatment of radiation cystitis with hyperbaric oxygen. J Urol 1986; 27:271–272.
19. Rijkmans BG, Bakker DJ, Dabhoiwala NF, Kurth KH. Successful treatment of radiation cystitis with hyperbaric oxygen. Eur Urol 1989; 16:354–356.

20. Rubin P, Casarett GW. Skin and adnexa. In: Rubin P, Casarett GW, eds. Clinical radiation pathology. Philadelphia: WB Saunders, 1968.
21. Heimbach RD. Radiation effects on tissue. In: Davis JC, Hunt TK, eds. Problem wounds: the role of hyperbaric oxygen. New York: Elsevier, 1988:53–63.
22. Marx RE, Ames JR. The use of hyperbaric oxygen in bony reconstruction of the irradiated and tissue-deficient patient. J Oral Maxillofac Surg 1982; 40:412–420.
23. Marx RE, Enler WJ, Tayaponsak P, Piere LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg. 1990; 160:519–524.
24. Perez CA, Brady LW. Overview. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. Philadelphia: JB Lippincott, 1992:53–55.