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Case Series: A multidisciplinary approach to the management of three cases of radiation induced angiosarcoma of the breast.

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Abstract

Radiation induced angiosarcoma (RIAS) is a rare, aggressive tumor of endovascular origin that arises in the breast tissue or chest wall of patients previously treated for breast cancer with radiation. Currently, there is no standardized therapy for RIAS, given its low incidence. We report the treatment of three patients with RIAS. These cases provide a useful framework, from initial presentation to follow-up, for providers regarding multidisciplinary management of RIAS.

Key words: radiation induced angiosarcoma, breast cancer, breast radiation

Introduction

Radiation induced angiosarcoma (RIAS) is a rare, aggressive tumor of endovascular origin that arises in the breast tissue or chest wall of patients with a history of breast cancer previously treated with adjuvant radiation. RIAS is typically a late sequelae of adjuvant radiation with a median latency period of seven years (Seinen). The first case of radiation induced sarcoma of the breast was described over three decades ago (1987, Body et al), however the prognosis remains poor, with median survival of 1-3yrs (Seinen, Monroe, Farran). Most practitioners have little experience with RIAS, given its low incidence (incidence 0.05-0.9% in patients treated with adjuvant radiation therapy) (Yap, Monroe, Sheth, Torres, West, Cohen-Hallaleh). However, over the last several decades, treatment of early stage breast cancer has shifted from modified radical mastectomy (MRM) towards breast-conserving therapy (BCT), possibly leading to an increasing incidence in RIAS (Cohen-Hallaleh, Sheth). RIAS represents a therapeutic challenge to providers as there is no standardized therapy regimen currently. The low incidence of RIAS has essentially precluded randomized controlled trials. We report three cases of RIAS that provide a useful framework for multidisciplinary treatment and emphasize the importance of coordinated cancer care from initial presentation to follow-up.

Methods:

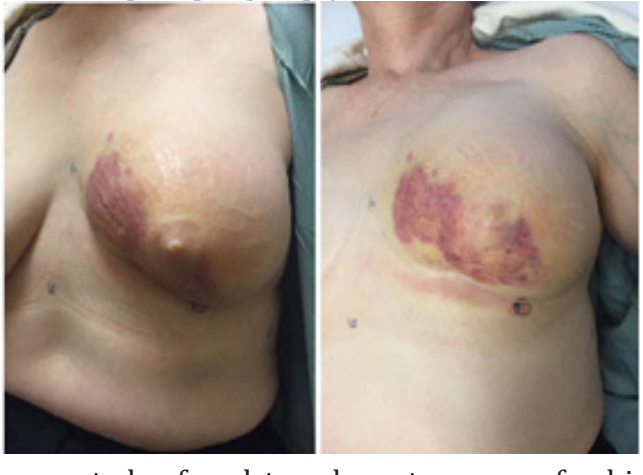
Three cases were selected to highlight the multidisciplinary approach our institution utilized in the treatment of RIAS. Clinicopathologic variables were collected and analyzed including: date of radiation therapy completion, age at time of RIAS diagnosis, neoadjuvant treatment, type of operation, margin status, tumor grade, tumor size, time from diagnosis to surgery, time to negative margins, time until complete wound healing, presentation at a multidisciplinary tumor conference, timing of initial consultations with plastic surgery

and medical oncology, adjuvant therapy, local recurrence, treatment of local recurrence, metastasis, treatment of metastasis and last follow-up.

Case Report 1

Our first patient is a 65-year-old female with a history of bilateral DCIS diagnosed in 2006 treated with BCT and right-sided invasive ductal carcinoma diagnosed in 2011. The right breast cancer was treated with neoadjuvant chemotherapy, wire-localized excisional biopsy with sentinel lymph node biopsy, and adjuvant trastuzumab and radiation therapy. The patient was clinically well until November 2016 when her medical oncologist noted erythematous skin changes and a small lump on her left breast. The skin changes (figure 1),

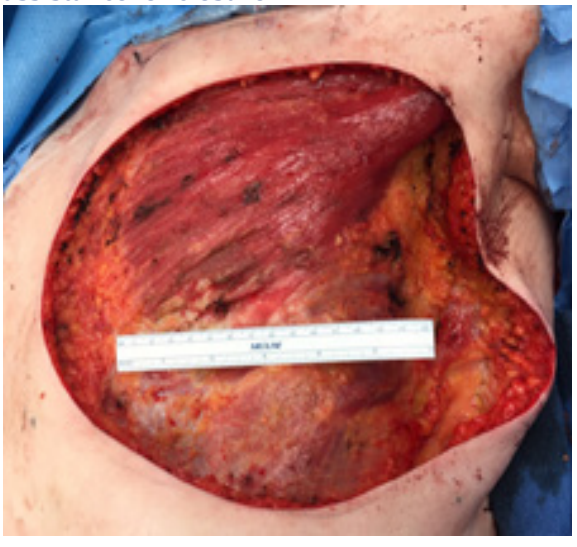
Figure 1: Case 1: Skin changes in previously irradiated breast, prompting biopsy.



prompted referral to a breast surgeon for biopsy, which demonstrated atypical endothelial cells and vascular channels with c-myc positivity, consistent with RIAS. PET-CT scan was performed and was negative for metastatic disease. Breast MRI was obtained and demonstrated skin thickening with nodular enhancement of the inferior and medial aspects of the left breast over a 7cm area. There was no lymphadenopathy or concerning changes in the right breast.

The patient was taken to the operating room for left non-skin sparing mastectomy with primary closure of the defect using local advancement flaps. However, at the time of surgery the residual defect was found to be too large to close with local tissue re-arrangement (20x27cm) (figure 2), therefore plastic surgery was consulted intra-operatively. Ultimately a latissimus flap was performed for soft tissue coverage.

Figure 2: Case 1: Soft tissue defect requiring plastics assistance for closure.



Pathology demonstrated a 13.5cm area of intermediate grade angiosarcoma with positive margins over a 6cm front along the medial border. The patient underwent re-excision of this medial border with temporary closure using a negative pressure system performed by breast and plastic surgery. The re-excision specimen was negative for residual angiosarcoma. The patient desired reconstruction and subsequently underwent reconstruction with DIEP flap and dermal graft a month after her initial mastectomy. Unfortunately, approximately four months after her initial resection, the patient noted a new erythematous area on the medial side of her right breast. Punch biopsy of the lesion was obtained and was consistent with angiosarcoma. CT scan at this time was negative for metastatic disease. The patient was started on propranolol and cyclophosphamide. The area of erythema regressed after two months of this regimen. She achieved 18 months of control with these medications, however her RIAS eventually progressed. She was switched to 9 months of paclitaxel, but eventually progressed on this regimen as well. She was then trialed on bevacizumab but had subsequent rapid progression of disease. Eribulin and pembrolizumb were not effective. She is currently on adriamycin, three years out from her initial presentation. In this case report, lack of pre-operative multi-disciplinary planning resulted in a large intra-operative defect without a pre-determined plan for closure. This ultimately led to recurrence in the setting of an autologous flap.

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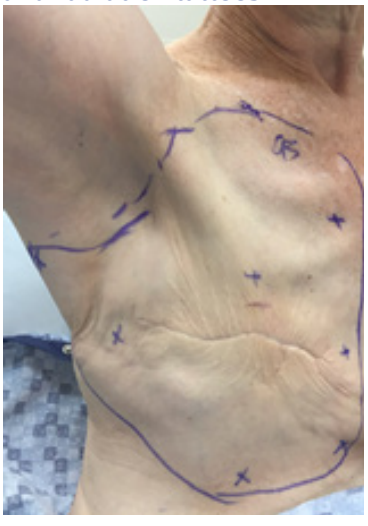
Case Report 2

A 65-year-old post-menopausal female with history of right breast cancer in 2001 treated with BCT, adjuvant chemotherapy (cyclophosphamide, methotrexate, fluorouracil), and five years of anastrozole presented to an outside clinic in 2015 with purple discoloration of the right nipple. There was initially concern for Paget's disease. Core needle biopsy was performed and demonstrated "deep dermal infiltrate of atypical epithelioid cells" but was inconclusive. Mammography was significant for peri-areolar skin thickening (BI-RADS 4). Skin changes progressed over the next month and the patient was referred to our clinic for evaluation. An excisional biopsy was performed by the breast surgery team. Pathology displayed CD31 and CD34 positivity consistent with angiosarcoma. Staging CT chest/abdomen/pelvis (CT C/A/P) was negative for metastatic disease. A right mastectomy with primary closure was performed. Final pathology revealed an intermediate grade 3.5x2x1.4cm angiosarcoma with negative margins greater than 2cm. The patient was referred to medical oncology post-operatively and followed with physical exam and chest CT every three months.

Approximately two years after her mastectomy, the patient noted a non-mobile, subcutaneous nodule on her chest wall near her incision, which increased in size. The patient subsequently re-presented and underwent punch biopsy, revealing recurrent angiosarcoma. CT C/A/P demonstrated skin changes of the right chest but was otherwise negative. MRI of the chest was also obtained and was negative for metastatic disease. Patient was seen by breast surgery and plastic surgery for pre-operative planning of chest wall resection. On the day of surgery, the planned area of resection was marked in pre-op, with special attention to include the patient's radiation tattoos and scars from prior excision with a gross 2cm margin from each (Figure 3).

Figure 3: Case 2: pre-operative marking for re-excision of recurrent angiosarcoma. Marking was made to include at least 2 cm margin from all prior scars and radiation tattoos.

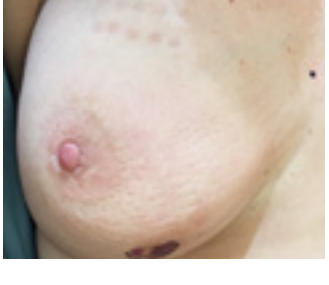


Following wide excision of the right chest wall skin and subcutaneous tissue, plastics partially closed the wound with an abdominal tissue advancement flap and application of a negative pressure system, with plans for definitive closure once margins came back negative. Pathology returned with an 8x9 cm area of scattered foci of disease with negative margins. The patient did not want reconstruction; therefore, the right chest wall was simply closed with a split thickness skin graft by the plastic surgery team. Decision was made in conjunction with medical oncology to continue surveillance every three months without any additional adjuvant treatment and the patient remains disease free at most recent follow-up, 57 months after initial RIAS diagnosis and 33 months after her local recurrence. In this case, all participating specialties were involved prior to excision which allowed for an adequate resection, closure, and follow up.

Case Report 3

A 60-year-old female with history of right breast cancer in 2015, treated with BCT and tamoxifen, noted several violaceous lesions on her inferior right breast in 2018 (figure 4).

Figure 4: Case 3: Initial presentation of RIAS



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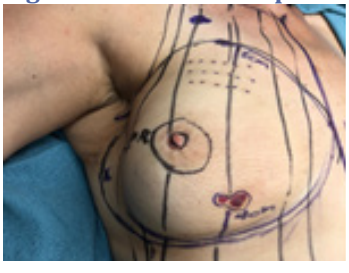
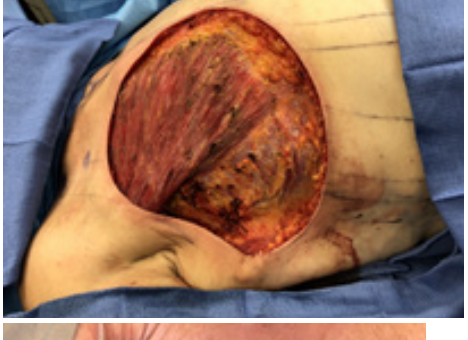
Punch biopsy demonstrated an atypical vascular proliferation consistent with RIAS (c-myc+, CD31+). The patient was referred for further management where she met with a breast surgeon, plastic surgeon, and medical oncologist. Staging CT scan demonstrated a 1.5cm soft tissue nodule in the right breast but no distant disease. The patient was marked pre-operatively to include at least 2cm from all radiation tattoos and skin lesions (figure 5).

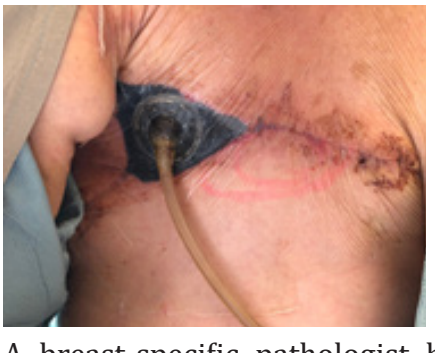
Figure 5: Case 3: Pre-operative marking



The patient underwent right mastectomy with sizeable resection of her right chest wall skin and subcutaneous tissue and abdominal tissue advancement flap with negative pressure system (Figure 6 A/B).

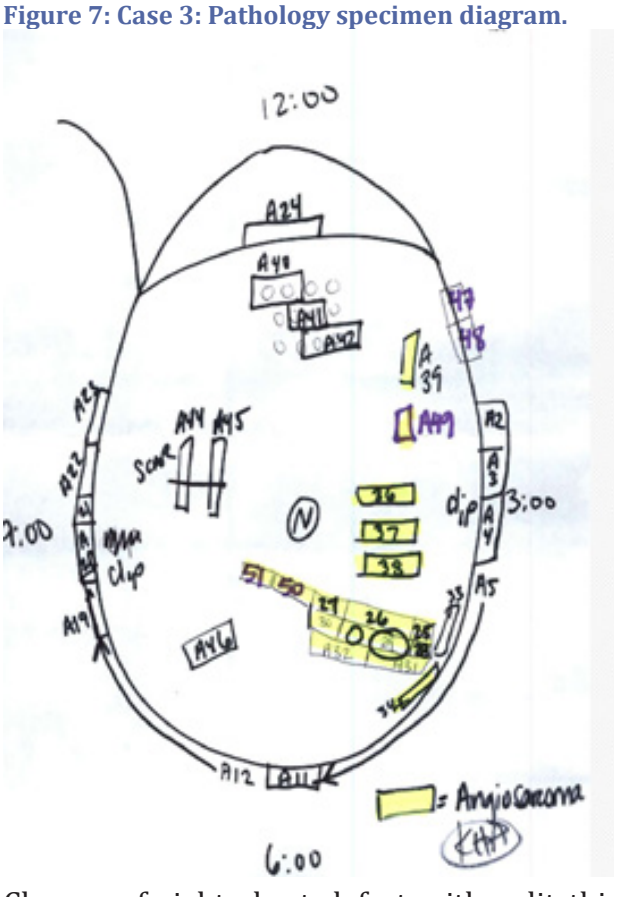
Figure 6: Case 3: A: large tissue defect after total mastectomy. B: temporary closure by plastic surgery with reverse abdominoplasty/abdominal tissue advancement flap with negative pressure system.





A breast-specific pathologist had been identified pre-operatively and was present in the operating room during specimen orientation by the breast surgeon. Pathology revealed a 11.2x9.5cm area of disease with clear margins (closest margin 3mm). The pathologist provided a detailed diagram of the specimen for the surgical team (Figure 7).

Figure 7: Case 3: Pathology specimen diagram.



Closure of right chest defect with split thickness skin graft was performed by plastic surgery once pathology report returned with negative margins. The patient has close surveillance by her medical oncologist with CT every six months. The patient remains disease free at most recent follow-up, nearly two years after initial diagnosis. This case again highlights an excellent outcome with the use of multidisciplinary planning.

Discussion:

Radiation induced angiosarcoma (RIAS) is an aggressive and rare tumor that can be difficult to diagnose. The mean age of presentation is in the sixth or seventh decade of life (50s-60s) (Seinen, Farran), consistent with our study population. Typical latency period is 4-10 years. The patient in case 3 is unusual in the fact that she presented within three years of her radiation treatment. However, this is not unprecedented, with some cases in the literature occurring within 6 months to 2 years of radiation treatment (Farran, Sheth, Chahin).

The initial presentation of RIAS is very diverse – from violaceous skin changes to blisters to induration. Diagnosis is sometimes

delayed when RIAS is confused for bruising, infectious erythema, or benign post-radiation treatment changes, therefore providers should have a high level of suspicion for RIAS when any patient with a history of breast radiation presents with skin changes and should refer their patient to a breast surgeon for punch biopsy early on.

Diagnosis requires an adequate tissue sample and expert pathologic analysis. Core needle, punch, or incisional biopsies are superior to FNA for diagnosis, as they provide adequate tissue sample with intact architecture (Sheth). A pathologist experienced in breast and/or sarcoma pathology should be available to examine biopsy and surgical specimens. The hallmark histologic finding of angiosarcoma is abnormal, pleomorphic endothelial cells (Farran). Biopsy specimens may demonstrate atypical vascular proliferation and positivity for endothelial markers like CD31 and CD34 (Monroe). C-MYC positivity (C-MYC oncogene amplification on chromosome 8q24.21) is a specific marker of RIAS, but has poor sensitivity (Farran, Lae). This c-MYC amplification is typically absent in sporadic angiosarcomas (Manner). Once diagnosis has been confirmed, multidisciplinary consultation, including medical oncology, breast surgery and plastic surgery should be initiated to coordinate a plan of care.

Early medical oncology involvement is essential. Patients require appropriate staging, evaluation for adjuvant treatment, consideration for enrollment in a clinical trial if indicated, and long-term follow-up for surveillance. In many cases it is the treating oncologist who first notes skin changes during follow-up visits for the initial breast cancer.

Barring any concerning symptoms, CT C/A/P or PET scan are adequate for pre-operative staging to rule out metastatic disease. There are no pathognomonic features of RIAS on imaging – often imaging of RIAS will appear normal or show non-specific skin thickening and post-treatment changes (Monroe, Chikarmane). Some suggest that breast MRI provides superior information regarding extent of disease compared to mammogram or ultrasound (Monroe). Breast MRI may also help to determine extent of the tumor and pre-operative planning (Sheth). Once imaging has been completed, a multidisciplinary discussion with involved providers should follow to determine next steps in care.

None of our patients were treated with neoadjuvant therapy. The only randomized trial examining neoadjuvant therapy in treatment of soft-tissue sarcoma was stopped early due to low enrollment, so for now, the role of neoadjuvant therapy remains in question (Gortzak, Sheth).

Prior to surgical resection, it is essential to determine the extent of resection required, estimate the size of resultant defect, and formulate a plan for closure. Based on our experience, we recommend that all cases of RIAS are reviewed with a plastic surgeon pre-operatively. A plastic surgery consultation allows for pre-operative discussions and planning regarding reconstruction options, as well as discussion about placement of a negative pressure system as a temporizing measure until final pathology results are known. If the defect is amenable to primary closure, that can be done at the time of resection. If a tissue flap or skin graft is needed to close the defect, placement of a negative pressure system is preferred and definitive closure with a skin graft or tissue is delayed until pathology results return, confirming negative margins. The patient in case 1 did not have a preoperative plastic surgery consultation, and was left with a large defect requiring an intraoperative consult for closure with a latissimus flap. She ultimately had to undergo excision of her latissimus flap due to positive margins from the initial resection. Pre-operative planning would have permitted a delayed closure until resection margins were negative.

Currently, surgery is the mainstay of curative treatment. The goal is an R0 resection, ideally with removal of all irradiated tissue. Radiation-induced sarcomas tend to occur at the margins of the previously irradiated field, where the radiation dose may be less than the tumor necrosis dose, thus producing survivable mutations that progress to tumor development (Jallali, Neuhaus). Many practitioners aim for 2-3 cm margins, although there are currently no guidelines for recommended margins (Cohen-Hallaleh). We mark our patients pre-operatively to include a 2cm margin from all radiation tattoos and skin lesions in an attempt to include

the entire irradiated field in the specimen. It is our practice to perform a completion mastectomy however wide local excision has also been reported. It has been our experience that the extent of RIAS is often much larger than initially indicated by skin deformities; or in other words, the skin changes may be just the tip of the iceberg. RIAS has a low likelihood of axillary metastasis, therefore SLNB and axillary dissections are not indicated (Torres, Sheth). Involvement of an experienced breast pathologist early on is essential for thorough examination of any resection specimens. Extra efforts are made to orient the specimen as specifically as possible, in event that margins are positive and additional resection is required. Once resection is complete, follow up with medical oncology is indicated for further surveillance and to determine need for adjuvant therapy.

The role of adjuvant treatment is unclear. In their review of 95 patients with RIAS, Torres et al found that patients who received chemotherapy had a statistically significant reduction in risk of local recurrence (Torres). The use of propranolol with traditional chemotherapy agents has shown promise (Pasquier). Beta-blockade has been shown to have a "suppressive" effect against angiosarcomas leading to a decrease in angiosarcoma tumor cell viability, decreased tumor growth in mice, and decreased tumor cell proliferation rates (Amaya). Propranolol is thought to potentiate the anti-proliferative and anti-angiogenic properties of certain chemotherapy agents (Pasquier). A suggested regimen includes propranolol 40mg BID plus a weekly chemotherapy agent (Pasquier). The patient in case 1 was maintained on this regimen for 18 months before recurring.

The benefit of adjuvant radiation for the treatment of RIAS is uncertain. There is concern for severe toxicity associated with re-irradiation, however some studies report decreased risk of local recurrence with the use of adjuvant radiation vs surgery alone (Riad, Torres). Yin et al report no significant survival difference in surgery plus adjuvant radiation versus surgery alone in treatment of RIAS (Yin).

Unfortunately, patients with RIAS frequently have local recurrence. Studies have shown that positive margins are associated with significantly higher risk of local recurrence, however, even with R0 resection, the incidence of recurrence remains high (Sheth, Barrow). It is often impossible to distinguish malignant tissue from normal tissue intra-operatively. Rather than being one uniform, contiguous mass, RIAS is often multifocal and has areas of disease peppered throughout the specimen. The propensity of this disease to form microstellite deposits likely contributes to an inability to obtain clear margins and local control (Cohen-Hallaleh, Torres, Seinen, Jallali). Monroe et al report a 73% recurrence rate in their review of 75 patients undergoing surgical resection (Monroe). Seinen et al reported local recurrence in nearly two-thirds of their patients despite R0 resection. Regardless, margins do seem to make a difference; in Cohen-Hallaleh's series of 49 patients with RIAS, resection margins in patients who went on to have local recurrence were significantly narrower than those who remained disease free (median clearance of 1.0 cm vs 2.5cm) (Cohen-Hallaleh). In D'Angelo et al's cohort analysis of 79 patients, univariate analysis demonstrated that resection margin status was the most important prognostic factor regarding distant recurrence-free survival (D'Angelo). Due to this high rate of recurrence, close follow-up is necessary.

Our patients are followed with a repeat clinical exam and CT C/A/P every 3-6 months. Recurrence can occur in a relatively short amount of time. The patient in case 1 had a local recurrence within 4 months of her initial resection. The majority of recurrences (84%) occur within one year of the initial surgery however, later recurrence is also possible, as seen in case 2 (Monroe).

Overall five-year survival rate for RIAS is quoted from 15-48% (Sheth, Cohen-Hallaleh, Monroe). In Dogan et al's review of the literature, they report a mean recurrence-free survival of 15.9 months and overall survival of 27.4 months (Dogan). In their review of 14 patients, Jallali et al report a median survival of 42 months for patients with complete excision whereas no patient survived beyond 15 months when complete excision of the primary tumor was not achieved.

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Several disease characteristics have been associated with worse outcomes including: tumor grade, presence of metastatic disease, and complete or no surgical resection (Sheth, Barrow). The number of skin lesions has also been shown to be an important prognostic factor - patients with multiple skin lesions have a 0% 2-year survival rate versus 50% for those with a single lesion (Sheth, Fodor). Tumor size is also an important prognostic factor with mean survival time of 80 months vs 20 months for patients with <2cm tumor and >5cm respectively (Sheth, Barrow).

The rarity of this disease, variable clinical findings, and aggressive nature make RIAS difficult to treat. Utilizing breast surgeons, plastic surgeons, specialized pathologists, and medical oncologists allows for the optimal multi-pronged approach to a formidable disease.

Conclusions

Although surgical resection is the mainstay of treatment for patients with RIAS, involving other disciplines is key to achieving the best possible outcomes in these difficult cases. In our experience, we found that management decisions for patients with RIAS should be made by a multidisciplinary team including a breast surgeon, plastic surgeon, oncologist, specialized pathologist, and in some cases, a radiation oncologist. All cases of RIAS should be reviewed with a plastic surgeon pre-operatively for wound closure planning and a discussion regarding reconstruction. Pre-operative medical oncology consultation is necessary to assess the utility of adjunct therapies. These cases provide a useful framework for providers treating RIAS, from initial presentation to follow-up.

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