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Prospective analysis of toxicity in patients treated with strut-adjusted volume implant for early-stage breast cancer

Sana Rehman[1], Reema Agarwal[1], Laura Ochoa[1], Pippa Cosper[1], Jacqueline Zoberi[1], Amy Cyr[2], Julie Margenthaler[2], Maria Thomas[1], Imran Zoberi[1,*]

[1]*Department of Radiation Oncology, Siteman Cancer Center, Washington University/Barnes-Jewish Hospital, Saint Louis, MO*
[2]*Department of Surgery, Siteman Cancer Center, Washington University/Barnes-Jewish Hospital, Saint Louis, MO*

ABSTRACT

PURPOSE: We report the toxicity of patients treated with strut-adjusted volume implant (SAVI) for accelerated partial breast irradiation treated at our institution.

METHODS AND MATERIALS: Patients treated from January 2013 to July 2015 with SAVI planned for 10 b.i.d. fractions for a total dose of 34 Gy were included. Acute and late toxicities were prospectively collected on patients in followup and graded by the Common Terminology Criteria for Adverse Events, version 4.0.

RESULTS: A total of 132 patients were included, with 1 patient having synchronous breast cancer treated in each breast. Median followup was 20.0 months (range, 2.7−37.4 months). The median age at diagnosis was 61 years (range, 41−83 years). Forty-two lesions (32%) were in situ, 88 lesions (66%) were Stage 1, and 3 (2%) lesions were Stage 2. The median planning target volume was 58.2 cc (range, 24.2−109.9 cc), median V_{150} was 26.3 cc (range, 11.5−47.5 cc), and median V_{200} was 13.0 cc (range, 6.3−26.1 cc). On a pain scale of 0−10 (10 = worst pain), pain was worst on Day 2 of treatment, with an average score of 0.46. There was one acute skin infection; there were three late skin infections, two of which was Grade 3. Other late toxicities were Grade 1 or 2: hyperpigmentation (44%), telangiectasia (0.8%), seroma (9%), fat necrosis (5%), and fibrosis (12%). Crude local recurrence rate was 4%.

CONCLUSION: SAVI is a safe treatment option for patients who are candidates for accelerated partial breast irradiation. Local control seems to be excellent, but longer followup is needed.

Keywords: Accelerated partial breast irradiation; Strut-adjusted volume implant; Breast cancer

Introduction

In 2016, in the United States, an estimated 246,660 women will be diagnosed with invasive breast cancer and an additional 61,000 women will be diagnosed with noninvasive breast cancer (1). Several trials with long-term followup have validated breast conserving surgery and adjuvant radiation therapy as an alternative approach to mastectomy for the management of early-stage breast cancer (2, 3, 4). The benefit of radiation therapy was confirmed in a meta-analysis that demonstrated adjuvant radiation therapy reduced the risk of recurrence and the risk of death from breast cancer (5). Adjuvant radiation therapy historically encompassed the whole breast, but certain patients are considered appropriate candidates for accelerated partial breast irradiation (APBI), where not only is the volume of breast being treated reduced, but the length of treatment is shortened.

Data comparing whole breast irradiation (WBI) to APBI continue to mature and provide information regarding side effects and tumor control outcomes. The Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial compared patients treated with WBI vs. APBI with external beam radiation therapy (EBRT) to 38.5 Gy in 10 twice daily fractions. This report found worse cosmesis at 3 years and higher rates of Grade 1 and 2 toxicities in the APBI

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* Corresponding author. Department of Radiation Oncology, Siteman Cancer Center, Center for Advanced Medicine, Washington University, Campus Box #8224, 660 S. Euclid Ave., St. Louis, MO 63110. Tel.: (314)-747-7236; fax: (314)-747-5736.

E-mail address: izoberi@radonc.wustl.edu (I. Zoberi).

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arm compared to the WBI arm (6). In contrast, Polgar *et al.* published a trial where patients were randomized to WBI vs. APBI with multicatheter interstitial brachytherapy. After a median followup of 10 years, good or excellent cosmetic outcomes favored the APBI arm (7). More recently, Groupe Européen de Curiethérapie−European Society for Radiotherapy and Oncology (GEC-ESTRO) published their Phase 3 results comparing APBI (with interstitial multicatheter brachytherapy) to WBI. A total of 1184 patients were accrued with median followup of 6.6 years. The 5-year local recurrence rate was not different between the two arms (0.92% vs. 1.44%); there was no difference in lymph node recurrence, disease-free survival, or overall survival. Regarding toxicity, at 5 years, there was no difference in Grade 2−3 late skin side effects or Grade 2−3 subcutaneous tissue side effects for WBI and APBI (8).

These data lend support to the use of APBI for properly selected patients. Strut-adjusted volume implant (SAVI) is another technique used for APBI, although there is less robust long-term data with SAVI, and no randomized prospective data comparing WBI to APBI with SAVI. Treatment with SAVI has been implemented in our institution since 2013 for delivery of APBI. SAVI has a central catheter with 6, 8, or 10 catheters on the periphery. SAVI has potential advantages over other methods of delivering APBI in its ability to conform the dose better around the target and spare skin and the chest wall, therefore minimizing toxicity. Yashar *et al.* published outcomes for a series of 102 patients treated with SAVI with a median followup of 21 months. The most common toxicity reported was hyperpigmentation (in less than 10% of patients), and the recurrence rate was 1% (9). Yashar *et al.* subsequently published (in abstract form) the results of 200 patients with median followup of 52.3 months. Late grade ≥2 toxicity was low (less than 5%), cosmesis was excellent (>93% reported good or excellent), and 4-year actuarial rates of local recurrence (either true recurrence or marginal miss) was 1.8% (10). The largest report available is from the SAVI Collaborative Research Group (abstract form) on 596 patients with a median followup of 39 months, which again confirmed excellent local control with low rates of late toxicity (11). With our present study, we aim to summarize our institutional experience with SAVI and report toxicity and preliminary local control results to contribute to the published SAVI data.

Methods and materials

An institutional review board-approved retrospective review was performed on patients treated with APBI using the SAVI device. The first patient at our institution was treated in January 2013, and we included patients through July 2015. A total of 133 cancers in 132 patients were included; 1 patient who was diagnosed with synchronous left and right breast cancers and underwent SAVI treatment to each breast. All patients had at least 30 days of followup, either with radiation oncology, medical oncology, and/or a surgeon.

Surgical management

All patients underwent a lumpectomy. All patients with invasive cancer underwent a sentinel lymph node biopsy, except for 1 patient. Patients with in situ disease did not undergo a routine sentinel lymph node biopsy. One patient had microscopic tumor cells in the nodes. Surgical margins were negative but close (≤1 mm) in 1 patient; the remainder of patients had negative margins either at the time of initial lumpectomy or following re-excision for close or positive margins.

Radiation therapy

Patients were evaluated by a radiation oncologist after the patient's definitive breast conserving surgery. The decision for the patient to undergo APBI was at the discretion of the treating radiation oncologist, based on our institutional guidelines for patients suitable for APBI. In general, our institutional APBI criteria include the following: age ≥40 years, tumor ≤3 cm, negative margins, node negative, unifocal tumor, ductal carcinoma in situ allowed if ≤ 3 cm, no lymphovascular space invasion, no neoadjuvant systemic therapy, and treated with APBI within 8 weeks of breast conserving surgery. No patients were known to have a deleterious BRCA mutation. Placement of the SAVI brachytherapy device was performed by the radiation oncologist via ultrasound guidance and local anesthetic in the outpatient setting. The SAVI is available in a variety of sizes categorized based on the number of peripheral catheters surrounding a central catheter (6−1 mini, 6−1, 8−1, or 10−1). The size of implant used, orientation, and positioning were based on estimation of cavity size and location determined by ultrasound and SAVI prep balloon. After insertion of the SAVI, a CT simulation was performed.

A planning target volume (PTV) was created from the tumor bed with a 1-cm expansion. This volume was edited to exclude the chest wall, the skin minus 5 mm, and the volume of the implant to create a new structure called PTV_eval. The prescription dose was 34 Gy delivered in 10 fractions given twice daily (3.4 Gy per fraction) separated by approximately 6 hours. The plan was optimized for coverage of the PTV_eval. Treatment goals included covering 90% of the PTV_eval with 100% of the prescription dose, covering 95% of the PTV_eval with 95% of the prescription dose, and covering 100% of the PTV_eval with 90% of the prescription dose. Further treatment goals included keeping the volume receiving ≥150% of the prescription dose or more below 50 cc and the volume receiving ≥200% of the prescription dose below 20 cc.

Patients generally started treatment within 2 working days of SAVI placement. Imaging consisting of plain films

or CT scan was performed before every fraction. On the day of the first fraction, a CT scan was performed to verify SAVI position. Afterward, repeat CT scan was only performed to verify positioning if there was concern for significant movement and potential under or over dosing.

Toxicity

Patients were asked their current pain level, worst pain in the past 24 hours, and least pain in the past 24 hours on the day of SAVI placement and on each fraction date. Pain was rated on a scale of 0 (no pain) to 10 (worst possible pain). Patients were also asked to rate their fatigue level on a scale of 0−4 (0, none, able to perform daily activities; 1, able to perform daily activities with rest periods; 2, must curtail daily activities even with rest periods and earlier bedtime; 3, unable to maintain daily activities, only short episodes of activity; and 4, confined to bed). Acute and late toxicities were recorded as reported in followup notes or imaging available and graded per the Common Terminology Criteria for Adverse Events, version 4.0. Fat necrosis was reported using the scale published by Garsa *et al.* (12)

Followup

After completion of radiation therapy, patients were generally examined after 1 week for a skin check then routine followup with history and physical examination (with surgery, medical oncology, and/or radiation oncology) and yearly mammography.

Results

A total of 132 patients were included in this study, with 1 patient having bilateral synchronous tumors that were both treated with SAVI (i.e., 133 SAVI implants). The median age at the time of diagnosis of the cohort was 61 years old (range, 41−83), with a median followup of 20.0 months (range, 2.7−37.4). Patient characteristics are given in Table 1. Based on the American Society for Radiation Oncology consensus guidelines (12, 13), 42 (32%) patients would fall into the suitable category, 71 (54%) patients would fall into the cautionary category, and 19 (14%) patients would fall into the unsuitable category. Of the patients in the unsuitable category, 18 patients were unsuitable because of age less than 50 years old (range, 41−49). One patient was unsuitable because she had invasive disease and did not have surgical nodal evaluation.

Table 1
Patient characteristics

Characteristics	Patients (n = 132); tumors (n = 133)
Median age (y, range)	61 (41−83)
Menopausal status (%)	
Post	106 (80)
Pre/peri	26 (20)
Race/ethnicity	
Black	23 (17.4)
White	106 (80)
Other	3 (2.3)
Smoking status (%)	
Current	12 (19)
Former	40 (30)
Never	80 (61)
Median noninvasive or invasive tumor size (cm, range)	1.0 (0.1−3)
In situ disease (%)	
DCIS alone	42 (32)
DCIS present with invasive disease	57 (43)
LCIS present	18 (14)
Invasive disease (n = 91, %)	
Ductal	68 (75)
Lobular	10 (11)
Other	12 (13)
Unknown	1 (1)
Grade (%)	
1	50 (38)
2	49 (37)
3	33 (25)
Unknown	1 (1)
Receptor status (%)	
Estrogen receptor positive	115 (86)
Progesterone receptor positive	110 (83)
Her-2 neu amplified	3 (2)
ASTRO guidelines	
Suitable	42 (32)
Cautionary	71 (54)
Unsuitable	19 (14)
Systemic therapy	
Chemotherapy	15 (11)
Hormonal therapy	100 (75)
Trastuzumab	2 (1)

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; ASTRO = American Society for Radiation Oncology.

Radiation therapy

Patients started radiation treatment a median of 26 days (range, 7−45) after their most recent surgery (either date of primary surgery or re-excision surgery for close or positive margin). One patient elected to discontinue radiation treatment after 1 day (and delivery of two fractions for a total of 6.8 Gy) after changing her mind about receiving adjuvant therapy; the patient declined further radiation therapy. All other patients completed the prescribed 34 Gy. One patient was delayed a single fraction, and the remainder of patients received radiation without interruption. Thirty (23%) 6−1 mini SAVI, 38 (29%) 6−1 SAVI, 27 (20%) 8−1 SAVI, and 38 (29%) 10−1 SAVI were placed. Dosimetric values for the PTV_eval are listed in Table 2.

Systemic therapy

Fifteen (11%) patients received adjuvant chemotherapy, which was generally initiated 3−4 weeks after completion of SAVI radiation treatment. Thirteen of those patients

Table 2
Dosimetric results

Volume	Median (range)
PTV_eval volume	58.2 cc (24.2–109.9 cc)
PTV V_{90}	98.6% (89.7–100%)
PTV V_{95}	96.4% (85.4–99.7%)
PTV V_{100}	92.3% (80.8–98.6%)
PTV V_{150}	26.3 cc (11.5–47.5 cc)
PTV V_{200}	13.0 cc (6.3–26.14 cc)

PTV = planning target volume; PTV_eval = planning target volume used for evaluation; V_{90} = volume covered by 90% of the prescription dose; V_{95} = volume covered by 95% of the prescription dose; V_{100} = volume covered by 100% of the prescription dose; V_{150} = volume covered by 150% of the prescription dose; V_{200} = volume covered by 200% of the prescription dose.

received taxane-based chemotherapy. One patient received cyclophosphamide, methotrexate, and fluorouracil chemotherapy for three cycles then discontinued chemotherapy. One patient received doxorubicin and cyclophosphamide for two cycles then discontinued chemotherapy. One hundred (76%) patients initiated adjuvant hormonal therapy. Two of the three patients with her-2 neu–amplified disease received her-2 neu–targeted therapy.

Toxicity

Twenty-one patients had no data regarding pain (scored from 0 to 10) recorded in the radiation oncology medical record; therefore, pain score results presented are from the remaining 111 patients who had at least one pain recording on the day of SAVI placement and on at least 1 day of treatment. One patient discontinued treatment after the first day of treatment (her pain score was not recorded in the medical record). The mean current pain on the day of SAVI placement was 0.067 (standard deviation [SD], 0.294), 0.407 (SD, 0.906) on Day 1 of treatment, 0.415 (SD, 0.932) on Day 2 of treatment, 0.247 (SD, 0.596) on Day 3 of treatment, 0.394 (SD, 0.975) on Day 4 of treatment, and 0.257 (SD, 0.783) on Day 5 of treatment. Median and mode score for pain were 0 on all 5 days. Figure 1 shows the trend of mean pain scores through the course

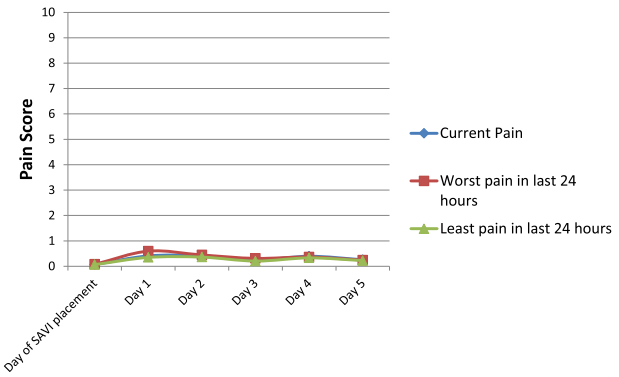

Fig. 1. Mean pain score trends from day of SAVI placement through the course of treatment. SAVI = strut-adjusted volume implant.

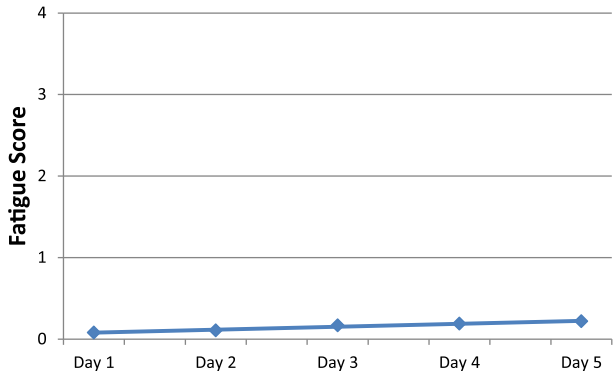

Fig. 2. Mean fatigue score trends through the course of treatment.

of treatment. Thirty-five (27%) patients reported taking some type of pain medication during the course of treatment (either over the counter or prescription medication). Fatigue score (scored from 0 to four) from at least 1 day of treatment was available for 108 patients. Figure 2 shows the trend for the mean fatigue score, which was 0.080 on Day 1 of treatment and 0.218 on Day 5 of treatment (median and mode = 0 for all days of treatment).

Four patients (3%) developed an infection (either acute or late) that may have been related to radiation. One was noted to have an infection at followup 1 month after completion of radiation therapy and was treated with antibiotics. One patient presented with infection 9 months after completion of therapy and was treated with antibiotics; this patient did not receive chemotherapy and was taking anastrozole. Two patients developed Grade 3 infections. The first patient presented with an infection 6 months after completion of radiation therapy and required operative incision and drainage. The second patient developed an infection 21 months after completion of radiation therapy. The patient was first tried on a course of antibiotics and then underwent an operative open breast abscess incision and drainage. Other late toxicities include 12 (9%) patients who developed a seroma (all Grade 1) based on physical examination or imaging. Seven (5%) patients developed fat necrosis based on imaging or physical examination (Grade 1 in 5 patients, Grade 2 in 1 patient, requiring nonnarcotic analgesics). Other late toxicities included (all Grade 1 or 2): 1 (0.8%) patient with telangiectasia, 16 (12%) patients with fibrosis, and 58 (44%) patients with hyperpigmentation at some time after completion of radiation therapy. It was unable to be ascertained if and by what degree the hyperpigmentation improved with time.

Tumor control

Five patients (4%) developed a local recurrence (four invasive and one noninvasive) at a median of 23 months after completing radiation therapy. Based on the American Society for Radiation Oncology guidelines, 2 patients were suitable candidates, 1 patient was cautionary (due to age

between 50 and 59 years), and 2 patients were unsuitable (due to age <50 years). One patient developed an ipsilateral invasive breast cancer at 24 months adjacent to the index cancer site and was salvaged with partial mastectomy followed by WBI. A second patient developed an ipsilateral invasive breast recurrence at 23 months and was salvaged with a mastectomy (showing multifocal disease) and did not require adjuvant radiation therapy. One year later, she developed chest wall and distant disease and was initiated on chemotherapy. A third patient developed ductal carcinoma in situ near the tumor bed at 6 months and was salvaged with a mastectomy. A fourth patient developed an ipsilateral invasive breast recurrence at 19 months and was salvaged with a mastectomy. The last patient developed an ipsilateral invasive breast recurrence (in a different quadrant from the index tumor site) at 23 months and was salvaged with a mastectomy. There were no regional or distant recurrences. One patient, with multiple medical comorbidities, passed away when she presented to the emergency room with dyspnea and ultimately had pulseless electrical activity. She had no evidence of disease at that time. No other patients died in followup.

Discussion

For women who opt to undergo breast conserving surgery, the majority are appropriate candidates for adjuvant breast irradiation. One report indicated that 86% of women received radiation therapy after breast conserving therapy (14), but another report demonstrated that there is variation in the number of women receiving adjuvant radiation therapy based on distance from a radiation therapy center (55% of women living ≥50 miles from a radiation center received adjuvant radiation, albeit the number of women who fit this criteria were small) (15). Lack of access to a radiation facility and the protracted course of treatment may negatively impact a woman's decision to undergo adjuvant radiation therapy.

Therefore, strategies such as APBI have been implemented to address these issues. This technique is advantageous in that it allows fewer trips to a radiation facility, making the treatment more convenient for patients. In addition, a smaller volume of normal tissue is irradiated, potentially decreasing the toxicity profile of breast irradiation. The most common area of a true local recurrence is within or near the original tumor bed (16), strengthening the argument of treating the area of the breast at highest risk of recurrence rather than treating the entire breast.

In addition to tumor control, toxicity and cosmesis remain important end points. An advantage in treating smaller volumes is that less breast tissue is irradiated, and there is a reduction in dose to critical organs such as the heart and lung, potentially decreasing the rate and grade of acute and late toxicity as well as improving breast cosmesis. The RAPID trial enrolled women with tumors ≤3 cm status postbreast-conserving surgery who were randomized to APBI (with 3D-CRT to 38.5 Gy in 10 b.i.d. fractions) vs. WBI. An interim analysis showed at 3 years worse adverse cosmesis in the APBI arm (29% vs. 17%, $p < 0.001$), which persisted at 5 years (33% vs. 13%, $p < 0.001$) (6). However, treatment with external beam APBI tends to treat larger volumes than interstitial or intracavitary techniques. A GEC-ESTRO study showed comparable late side effects when comparing WBI with a boost (to a total dose of 60 Gy) vs. APBI (with multicatheter interstitial technique). At 5 years, the risk of Grade 2−3 late skin side effects was 5.7% vs. 3.2% ($p = 0.08$), and the risk of Grade 2−3 subcutaneous tissue effects was 7.6% vs. 6.3% ($p = 0.53$) for WBI and APBI, respectively (8).

Intracavitary and interstitial techniques circumvent some of the issues of EBRT by allowing for smaller expansions for the PTV volume and therefore having smaller PTVs. In addition with SAVI, there is flexibility in covering the target area while sculpting dose away from normal structures. However, data specifically on SAVI are sparse thus far. The SAVI Collaborative Research Group (comprised of 14 institutions with over 1000 patients in its registry) has published (in abstract form) the largest series of patients with clinical outcomes. The most recent report includes 596 patients with at least 12 months of followup. Good/excellent cosmesis was achieved in >94% of patients. Grade ≥2 late toxicity was less than 5% when combining telangiectasias, seroma, and fat necrosis (10). To our knowledge, outside from the SAVI Collaborative Research Group and the study from Yashar *et al.* (8−10), no institutions have published their results with SAVI. Our single-institution experience adds to the available data. From a toxicity standpoint, women tolerated the treatment very well. The average pain scores from Days 1 and 5 of treatment were 0.407 and 0.257, respectively (with a mode of 0). The average fatigue scores from Day 1 and 5 of treatment were 0.080 and 0.218 (mode = 0), respectively. These prospectively obtained values are near 0 (i.e., no pain and women continuing to be able to perform daily activities), supporting that in the acute setting the SAVI apparatus is very well tolerated with almost no impact on women. Late toxicity in this review includes 5% with fat necrosis, 2% with an infection (including two Grade 3 that required surgery), 9% with seroma, 0.8% with telangiectasia, 12% with fibrosis, and 44% with hyperpigmentation. Although there are a significant number of women who developed hyperpigmentation at some point after completion APBI, all were Grade 1 and did not require further intervention. In addition, it was not able to be determined how many of these women had hyperpigmentation that had resolved at further followup. Our data support a very favorable toxicity profile for SAVI.

The limits of our study are the retrospective nature, which makes it difficult to accurately assess acute and late toxicity. Although pain and fatigue were prospectively scored, there was no similar metric for cosmetic outcomes.

In followup for some patients, a breast toxicity form is filled out by a nurse practitioner, but this has not been routine practice for all patients. In addition, patient-reported cosmetic outcomes were not available. Regarding tumor control, this study has short followup (20.0 months). With further followup, more accurate reports of tumor control will be available, and in this study, we only report crude numbers of local recurrences.

The pending results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B39 trial will further elucidate the role of APBI, regarding both tumor control and side effects. Women eligible for this study had Stage 0, 1, or 2 breast cancer with a tumor size ≤3.0 cm status postlumpectomy. Patients were randomized to WBI (50−50.4 Gy with an optional boost to 60−66 Gy) vs. APBI. The techniques allowed for APBI include multicatheter brachytherapy, an intracavitary device (such as MammoSite), or EBRT; intraoperative methods were not included. The primary end point is diagnosis of in-breast tumor recurrence. When data from NSABP B39 mature, it will allow for further comparisons of the different techniques of APBI; however, the numbers of patients treated specifically with SAVI will likely be low, as most patients receiving APBI are treated with external beam radiation as it is the most commonly available technique. Therefore, once the results of B39 are available, it may only provide limited insight into SAVI treatment and thus emphasizing the importance of institutional studies reporting their experiences with SAVI, such as ours.

In conclusion, this study provides additional support for the SAVI apparatus for APBI. We await further followup from the GEC-ESTRO study and results from the NSABP B39 trial to provide more detail regarding APBI.

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