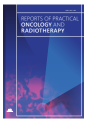

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REVIEW ARTICLE

A historical literature review on the role of posterior axillary boost field in the axillary lymph node coverage and development of lymphedema following regional nodal irradiation in breast cancer

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ABSTRACT

To elucidate whether (1) a posterior axillary boost (PAB) field is an optimal method to target axillary lymph nodes (LNs); and (2) the addition of a PAB increases the incidence of lymphedema, a systematic review was undertaken. A literature search was performed in the PubMed database. A total of 16 studies were evaluated. There were no randomized studies. Seven articles have investigated dosimetric aspects of a PAB. The remaining 9 articles have determined the effect of a PAB field on the risk of lymphedema. Only 2 of 9 articles have prospectively reported the impact of a PAB on the risk of lymphedema development. There are conflicting reports on the necessity of a PAB. The PAB field provides a good coverage of level I/II axillary LNs because these nodes are usually at a greater depth. The main concern regarding a PAB is that it produces a hot spot in the anterior region of the axilla. Planning studies optimized a traditional PAB field. Prospective studies and the vast majority of retrospective studies have reported the use of a PAB field does not result in increasing the risk of lymphedema development over supraclavicular-only field. The controversies in the incidence of lymphedema suggest that field design may be more important than field arrangement. A key factor regarding the use of a PAB is the depth of axillary LNs. The PAB field should not be used unless there is an absolute indication for its application. Clinicians should weigh lymphedema risk in individual patients against the limited benefit of a PAB, in particular after axillary dissection. The testing of the inclusion of upper arm lymphatics in the regional LN irradiation target volume, and universal methodology measuring lymphedema are all areas for possible future studies.

Key words: posterior axillary boost; breast cancer radiotherapy; axillary lymph node; regional nodal irradiation

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Introduction

The radiotherapeutic management of the regional lymph nodes (RLNs) for breast cancer patients remains important, but it is technically challenging. Traditional approach to treat supraclavicular (SC) fossa and axilla is the use of an anterior-posterior (AP, *i.e.*, anterior SC fossa field) and posterior axillary boost (PAB) field arrangement [1–3]. In other words, the majority of breast cancer patients with

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nodal involvement were treated with SC field alone or in combination with a PAB field. The goal of a PAB field arrangement is to ensure complete dose coverage of SC fossa and levels I/II/III axilla [3]. The majority of dose is delivered through a SC field prescribed to the depth of maximum dose or 3-cm depth to cover SC fossa and level III axilla [3]. However, more lateral level I/II axilla have a deeper location in comparison with the SC nodes. Therefore, sufficient dose may not be delivered to these regions. To ensure adequate coverage of level I/II axilla a PAB field is used.

Nevertheless, there are considerable debates regarding the effectiveness of a PAB field. To date, several studies have investigated dosimetric aspects of the PAB field and reported that it may not be an optimal technique to treat level I/II axillary LNs, in particular in the new era of breast cancer radiotherapy (RT) [1-4]. In addition, the effect of a PAB on lymphedema development in breast cancer patients remains incompletely understood. Lymphedema has an important effect on patient's quality of life (QOL) [5, 6]. Taken together, it is, therefore, important for radiation oncologists to clearly understand dosimetric and clinical aspects of a PAB field.

Therefore, the objectives of this literature review were (1) to evaluate whether a PAB field is an optimal method to target SC and axillary LNs; and (2) to investigate whether the addition of a PAB increases the incidence of lymphedema.

Materials and methods

Search strategy and selection criteria

PubMed database was used for the literature searching from January 1990 to December 2019 using the following search terms: *(Breast cancer radiotherapy) AND ("Posterior axillary boost" OR "Regional nodal irradiation" OR "Regional radiotherapy")*. The following selection criteria were adopted:

- inclusion criteria: studies on human, specifically investigating the dosimetric and clinical aspects or clinical efficacy of a PAB, full-text published articles in English;
- exclusion criteria: review articles, animal studies, lack of relevant outcome data, non-English written articles, editorials, commentaries, conference abstracts.

To select a full-text article for review, search results were screened based on title and abstract (Fig. 1). Outcomes were expressed as reported originally. However, meta-analysis and statistical analysis were not carried out because of the obvious heterogeneity of patient cohort in the selected articles and variation in the outcomes reported.

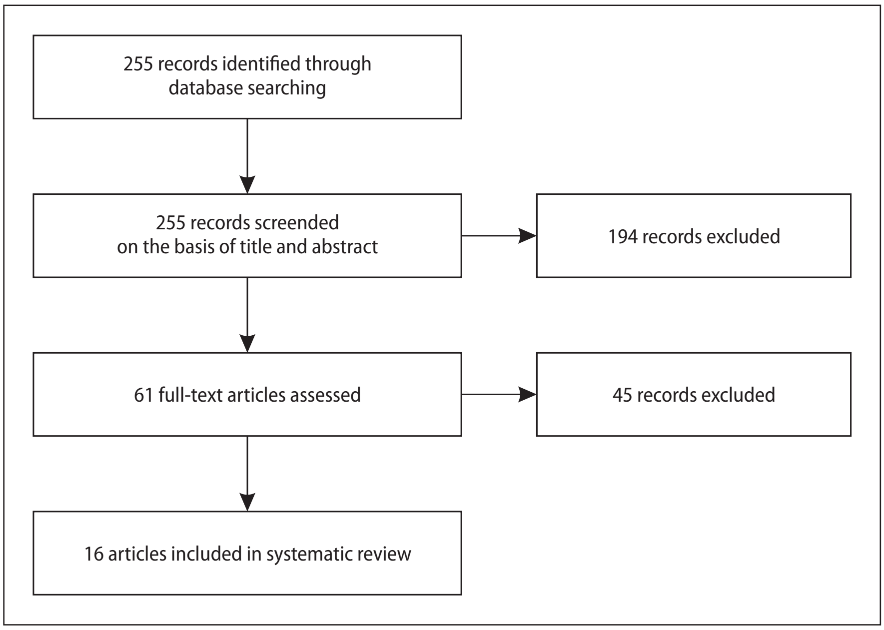

Figure 1. Flowchart for literature search

Results and discussion

Study selection and study characteristics

Two-hundred and fifty-five potentially relevant articles were identified and screened for title and abstract. Sixty-one full-text articles were evaluated for eligibility. Of these, 45 articles were excluded after full-text reading. Finally, a total of 16 articles that met the inclusion criteria were included in this literature review, as displayed in Figure 1. Seven articles have investigated dosimetric aspects of a PAB. The remaining 9 articles have determined whether the addition of a PAB field increases the risk of lymphedema. There were no randomized studies. Only 2 of 9 articles have prospectively reported the impact of a PAB on the risk of lymphedema development. Table 1 and 2 provide a summary of the characteristics of the included studies and their main outcomes.

Posterior axillary boost field

Historically, a PAB field was developed based on the fact that the axillary LNs are deeper than the SC LNs in the pre-computed tomography (CT) era [1]. On the other hand, if a SC field provides inadequate coverage of deep LNs owing to axillary node separation, then a PAB field may be used to assure optimal dose distribution in the mid-axillary area [3]. In some centers, a PAB field was added if there were gross extranodal spread of tumor, inadequate axillary dissection, positive axillary nodes, and axillary failure without previous history of irradiation [3, 8, 13]. The medial border of a PAB field is typically defined by 1.5 to 2 cm of the lung. The lateral border is at the posterior axillary fold; however, the posterior axillary fold is not a useful plain film or CT landmark. The inferior border will match the breast tangentials and superior border splits the clavicle. Also, the gantry may be tilted 10-15 degrees to spare the trachea, esophagus, and spinal cord. Of note, if the medial PAB border is defined by 2 cm of lung, there is no need for a gantry tilt. The prescribed dose is such that the combination dose distribution ensures adequate coverage of nodal volumes. There is an overlap between the anterior SC field and the PAB field with the amount of overlap varying from one patient to another. The borders of a PAB field may be edited to block hot spots owing to overlap with a SC field.

Dosimetric effect of posterior axillary boost field

Table 1 summarizes studies on dosimetric aspects of the PAB field in axillary LNs irradiation. A deep understanding about the depths of the SC and axillary LNs is an important step to elucidate the necessity of a PAB. Studies have reported that the depth of the SC and axillary LNs varies widely [1, 8]. In a study based on CT data, Bentel et al. measured the maximum depth of the SC and axillary LNs in 49 patients at the Duke University of Medical Center [1]. Furthermore, these authors determined the relationship between the SC and axillary LN depth and patient's size represented by the AP diameter. The median of the SC LNs depth was 4.3 cm in a range from 2.4 to 9.5 cm. The depth of the axillary LNs ranged from 1.4 to 8 cm, with a median of 4.3 cm. It was observed that the axillary LNs lie at approximately the same depth or shallower than the SC in most patients. The results of that study demonstrated that the dose to the axillary LNs was within ± 5% of the SC dose in 53% of patients and was 90% or more of the dose delivered in the SC in 90% of patients, when an anterior 6-MV beam only was employed to treat both the SC and axillary LNs. Therefore, they concluded that these results can obviate the need for a PAB field. As suggested by Bentel et al., the use of higher energy beams, an anterior beam only, or opposed fields may be reasonable when the SC and axillary LNs are deep [1]. Furthermore, a deeper prescription dose point can provide sufficient planning target volume (PTV) coverage for patients with deep nodal volumes, this, however, results in more intense hot spots. A concern regarding higher energy beam is potential underdosing of superficial LNs. When a high energy beam is employed, the placement of bolus on the SC region is necessary owing to the behavior of depth dose. Depth dose does not decrease in a linear fashion. As a result, the use of an anterior beam only is suboptimal in some cases. However, the anterior beam may be useful for selected patients with small separations. It is worthwhile to mention that patients with elevated separations that require high energy beams do not have superficial LNs.

In another study, Goodman et al. measured the depths of SC and level I-III axillary LNs relative to the anterior skin surface [8]. The median (range) depths of the SC and level I-III axillary LNs were 3.7

Table 1. Summary of studies on dosimetric aspects of a posterior axillary boost field

Author/year	Purpose of study	Main conclusion	Comment
Rajasekar et al. 1998 [7]	Reducing dose inhomogeneity in the axilla using a PTB	There is a dose variation (14-25%) in axilla when treated with a SC field and a PAB. This dose inhomogeneity can optimize using a PTB in the SC field corresponding to the diverging PAB field	Increasing complexity in the treatment by introducing a PTB
Bentel et al. 2000 [1]	Determining depth of SC and axillary LNs on CT data, and needs for a PAB field	The median of the SC LNs depth was 4.3 cm in a range from 2.4 to 9.5 cm. The depth of the axillary LNs ranged from 1.4 to 8 cm, with a median of 4.3 cm. There is considerable variation in the depth of SC and axillary LNs among patients. This variability depends on patient's size. Dose to axilla was 90% or more of the dose delivered in the SC in 90% (44 of 49) of patients when an anterior 6 MV beam only was used to treat SC and axilla, obviating the need for a PAB field	The use of higher energy beam may be an alternative way to a PAB when the SC and axillary LNs are deep
Goodman et al. 2001 [8]	Investigating the fields in which the SC and axillary LNs appear in the different RT techniques	The median (range) depths of the SC and level I-III axillary LNs were 3.7 cm (2.1–7 cm), 4.9 cm (1–12 cm), 5.1 cm (2.5–11.6 cm), and 3.2 cm (1.9–7.4 cm), respectively. There is considerable variation in the depth of SC and axillary LNs, as well as the fields in which nodal groups appear, specifically in the PAB field. No nodal groups in the PAB field were seen in the 6/55 patients	To treat some or all LNs in breast cancer it is important to know which LNs are appeared in different fields (*i.e.,* tangential fields, SC field, and PAB field). CT-scan is the most reliable method that can delineate nodal groups and determine their location
Jephcott et al. 2004 [9]	Determining the best treatment plan for SC and axillary regions	The APcom-PAB technique can provide a good PTV coverage (compared with AP-only), lower hot spots (compared with AP-PAB), and less medial posterior neck radiation (compared with AP-PA and AP-PAB)	In cases in which an AP technique alone cannot provide adequate coverage of nodal groups, an APcom-PAB technique can be used
Wang et al. 2009 [3]	Whether a PAB field is an optimum technique to treat SC and axillary LNs	The SC field with an AAB and IMRT resulted in reducing dose inhomogeneity and improving conformity compared with a PAB. The mean the treatment volume receiving 105% or greater of the prescribed dose (V105%) was 55.9 cc for AAB field and 70.0 cc for PAB technique ($p = 0.037$)	The PAB is a suboptimal technique to target SC and axillary LNs. The CT-based treatment planning along with dose optimization techniques can be a standard technique for regional LNs irradiation
Sethi et al. 2012 [4]	Determining optimal method to treat breast and SC and level III axillary LNs	An optimal target coverage and decreased ipsilateral lung V20 were achieved by prone IMRT. A 4-field supine 3DCRT using PAB resulted in an average of only 59% of the LN-PTV receiving 100% of the prescribed dose	IMRT improves regional nodal coverage, but may increase the risk of secondary malignancies owing to higher low radiation doses to normal tissues such as lung
Hernandez et al. 2013 [2]	Introducing an optimized PAB technique for targeting SC and axillary LNs	Optimized PAB provided adequate target coverage, less hot spots, and sufficient sparing of normal tissues compared with historically techniques such as AP-only, AP-PA, AP-PAB, and AP-AAB. The mean hot spot dose was 107.7% in the optimized PAB technique and 113.5% in the PAB technique ($p = 0.006$)	Optimized PAB technique is a simple, fast, and easy technique that can implement in the routine clinical practice

PTB — partial transmission block; SC — supraclavicular; LN — lymph node; CT — computed tomography; PAB — posterior axillary boost; RT — radiotherapy; APcom-PAB — anterior field with posterior boost field to the axilla with customized compensation of the anterior beam; PTV — planning target volume; AP — anterior-posterior; PA — posterior-anterior; AAB — anterior axillary boost; V20 — Volume receiving 20% of prescribed dose; IMRT — Intensity modulated radiotherapy; 3DCRT — three-dimensional conformal radiotherapy

Table 2. Summary of studies on the impact of a posterior axillary boost on lymphedema risk

Author/year	Location	Study period	No. of patients	Type of study	Median follow-up (months)	Method of measuring LE	Threshold for defining LE	Type of axillary LN surgery	Risk of LE
Chua et al. 2002 [10]	Westmead Hospital, Australia	1979–1994	1158	Retrospective	88	Arm circumference	≥ 2 cm	ALND or none	40% (6/15) and 31% (42/136) in patients with AX surgery + RT (B + SC) and AX surgery + RT (B + SC + PAB), respectively; not significant
Coen et al./ 2003 [11]	Massachusetts General Hospital, USA	1982–1995	727	Retrospective	39	Arm circumference	≥ 2 cm	ALND or none	1.8% (6/493) and 8.9% (15/234) in patients with B-only RT and B + SC + PAB RT, respectively; $p = 0.001$
Hinrichs et al. 2004 [12]	Roswell Park Cancer Institute, USA	1995–2001	105	Retrospective	24.4	Subjective	Physician impression	ALND	47.1% (8/17) in patients with PAB RT and 23% (20/87) in patients without PAB RT; $p = 0.047$. The use of a SC alone did not increase the risk of LE; $p = 0.245$
Hayes et al. 2008 [13]	Fox Chase Cancer Center, USA	1970–2005	2579	Retrospective	81	Subjective	Physician impression	ALND or SLNB or none	16% (355/2169), 23% (52/226), and 31% (57/184) in patients with B-only, B + SC, and B+ SC + PAB RT. **Odds ratio (95% CI)** SC *vs.* B-only: 2.147 (1.351–3.411); $p = 0.0012$ PAB *vs.* B-only: 3.181 (2.006–5.046); $p < 0.0001$. PAB *vs.* SC: 1.482 (0.927–2.370); $p = 0.1006$
Bar AD et al. 2012 [14]	Hospital of the University of Pennsylvania, USA	1977–2002	266	Retrospective	56	Arm circumference	≥ 2 cm	ALND or none	In Univariate Cox models, SC and PAB RT were significant risk factors for progression of LE; $p = 0.035$ and $p = 0.014$, respectively. No significant difference between patients in B + SC group and patients in B-only group; $p = 0.4$. A significant difference between patients in B + SC + PAB group and patients in B-only group was observed; $p = 0.01$
Shah et al. 2012 [15]	William Beaumont Hospital, USA	1980–2006	1497	Retrospective	NR	Subjective	CTCAE v2.0	ALND or none	7.3% (106/1453) and 14.7% (5/34) in patients with and without a PAB RT, respectively; $p = 0.1$
Warren et al. 2014 [16]	Massachusetts General Hospital, USA	2005–2012	1099	Prospective	25.4	Perometer	$\geq 10\%$ volume difference	SLNB or ALND or none	3.1%, 21.6%, and 20.9% in patients with B-only ($n = 790$), B + SC ($n = (194)$, and B + SC + PAB ($n = 115$) RT, respectively. No significant difference between SC and SC + PAB; $p = 0.96$

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Table 2. Summary of studies on the impact of a posterior axillary boost on lymphedema risk

Author/year	Location	Study period	No. of patients	Type of study	Median follow-up (months)	Method of measuring LE	Threshold for defining LE	Type of axillary LN surgery	Risk of LE
Chandra et al. 2015 [17]	Massachusetts General Hospital, USA	2005–2012	172	Prospective	29.3	Perometer	≥ 10% volume difference	ALND or SLNB or none	22.27% and 20.98% in patients with B + SC (n = 118) and patients with B + SC + PAB (n = 54), respectively. **Hazard ratio (95% CI)** SC *vs.* SC + PAB: 1.15 (0.61–2.16); p = 0.66
Gross et al. 2018* [18]	Robert H. Lurie Comprehensive Cancer Center, USA	1999–2013	492	Retrospective	66	Arm circumference	≥ 2.5 cm relative to a baseline obtained after surgery but before radiation therapy or ≥ 2 cm at 2 or more consecutive visits	ALND or SLNB	7.7%, 37.1%, and 36.7% in patients in Group 1 (n = 101), 2 (n = 202), and 3 (n = 189), respectively. There is a significant difference between Group 1 and Group 2 and 3; p < 0.0001 **Hazard ratio (95% CI)** Group 2 vs. Group 1: 4.73 (2.34–9.58); p < 0.0001. Group 2 vs. Group 1: 3.37 (1.58–7.2); p = 0.002

NR — not reported; LE — lymphedema; CTCAE — Common Terminology Criteria for Adverse Events; LN — lymph node; ALND — axillary lymph node dissection; SLNB — sentinel lymph node biopsy; AX — axilla; RT — radiotherapy; B — breast; SC — supraclavicular; PAB — posterior axillary boost. *Group 1 received a SC field that excluded the uppermost portion of the level I/II axilla but could include a PAB field (2 patients with PAB field), group 2 received radiation to the majority of the level I to III of the axilla with or without PAB (27 patients with PAB field), and group 3 received radiation to the entirety of the anterior and posterior axilla (no patients with PAB field)

cm (2.1–7 cm), 4.9 cm (1–12 cm), 5.1 cm (2.5–11.6 cm), and 3.2 cm (1.9–7.4 cm), respectively. In addition, these LNs were positioned well anterior to the midline. In fact, none of these nodes were posterior to the midline. Meanwhile, the dosimetric coverage of the SC and axillary LNs with standard breast tangents and nodal fields was assessed. As reported by Goodman et al., with the use of the standard radiation tangents 90% of the level I axillary LNs and up to 70% of level II axillary LNs received 95% of the prescribed dose to the breast [8]. The results showed that there was a considerable variation in the nodal groups present in the PAB field. In 6/55 patients were no nodal groups were observed in the PAB field [8]. Although the results of the study by Goodman et al. [8] are in good agreement with a previous study by Bentel and colleagues [1], it should be kept in mind that the level I axillary LNs rarely were in the anterior field in the Goodman et al. study [8]. Consistent with their findings, Pierce et al. reported that the level I axillary LNs were in the tangential fields and the apex of the axilla (the infraclavicular region) was treated through the SC field. However, the level II axillary LNs were partially covered in the SC field, and were often supplemented by a PAB field [19].

The PAB field provides a good coverage of the level I/II axillary LNs because these nodes are usually at a greater depth. Of note, in most of the patients, the PAB field results in a large high-dose region in the AP region of the axilla [2, 7, 9]. This is the most important drawback of this technique, as reported in several studies. To reduce and optimize excessive hot spots at the exit of the PAB field, several techniques have been introduced [2, 7, 9]. The core concept of these techniques was to compensate the overlap with the PAB port. Partial transmission blocks (PTBs) were used to attenuate the anterior field. Rajasekar et al. reported that there was 14-25% dose variation in the axilla when irradiated by an anterior field and a PAB field [7]. They suggested that using an appropriate PTB in the anterior SC field corresponding to the diverging PAB field can optimize these dose variations, with the fact that the axillary LNs are deeper than the SC LNs [7]. In another method, a customized compensator was applied to minimize undesirable hot spots in the anterior region of the axilla [9]. Jephcott and colleagues showed that the use of an anterior field with PAB field for treatment of the SC and axillary LNs in adjuvant RT can provide a good PTV coverage, but it produced an excessive hot spot (> 120%) in 90% of patients (9/10 patients) [9]. In an attempt to reduce hot spots, an anterior field with PAB field to the axilla with customized compensation of the AP beam (APcomp-PAB) was assessed. Using this new technique significantly reduced hot spots > 120% in all cases. Only in one case, was this new technique rejected owing to a high brachial plexus point dose. Also, the APcomp-PAB gave an adequate PTV coverage similar to an anterior field with PAB field [9]. However, the creation of PTBs and compensators is time-consuming and requires a mold room. Nowadays, three-dimensional (3D) printing technology can fabricate treatment and patient-specific devices [20]. Therefore, above-mentioned accessories can be generated by 3D printing technology that results in reducing time and cost. However, the addition of compensators and PTBs can lead to complexity in treatment planning. Above-mentioned techniques also increase the scatter dose received by the contralateral breast, and require an interruption in daily treatment fraction. It should be noted, however, that toxicity of increased scatter is not clinically relevant, especially since most compensation is electronic these days. Taken all together, these techniques are impractical for routine clinical use.

In an attempt to eliminate these drawbacks, Hernandez et al. have introduced an optimized PAB technique [2]. This technique was mainly based on the PAB technique, but the anterior field was split into two fields: a standard anterior field and another anterior field with the same gantry angle that shielded the region of overlap with the PAB field to decrease the hot spots. The optimized PAB technique provided adequate coverage of the SC and axillary LNs while minimizing radiation dose to the surrounding normal tissues. Furthermore, this technique overcame the main disadvantage of the PAB technique, *i.e.*, it reduced hot spots. The mean hot spot dose was 107.7% in the optimized PAB technique and 113.5% in the PAB technique (p = 0.006) [2].

Recent studies have indicated that the PAB field is a suboptimal technique for treating SC and axillary LNs and new techniques such as intensity modulated RT (IMRT) can provide the opportunity to optimize dose coverage and reduce radiation-induced damage to the surrounding healthy tissues [3, 4]. The results of the study by Wang et al. showed that CT-based techniques such as an SC field with an anterior boost field and IMRT resulted in superior dose coverage compared with PAB field [3]. In addition, superior lung sparing and dose conformity to the target were achieved by the IMRT technique. Authors also indicated that the use of the anterior axillary boost (AAB) field resulted in producing smaller hot spots (*i.e.*, 105% isodose) compared with the PAB field [3]. The mean the treatment volume receiving 105% or greater of the prescribed dose (V105%) was 55.9 cc for an AAB field and 70.0 cc for the PAB technique (p = 0.037). Of note, the PAB technique was not based on CT data, whereas the AAB technique was a CT-based treatment planning. In contrast, when both techniques were based on individual patient's anatomy, the AAB technique generated higher and larger hot spots; therefore, it is dosimetrically inferior compared to the PAB field, as reported by Hernandez and colleagues [2]. In another study, Sethi et al. compared several 3D techniques and IMRT for level III axillary LNs and SC LNs coverage [4]. Prone IMRT technique resulted in adequate nodal PTV coverage, and reduced ipsilateral lung V20. The results of that study revealed that a supine four-field 3D conformal RT (3DCRT) using PAB resulted in an average of only 59% of the LN-PTV receiving 100% of the prescribed dose [4]. Bentel et al. thought that covering LNs with 90% of the dose was good enough to justify omitting PAB [1]. In the study by Sethi et al., the PAB technique was criticized for covering only 59% of the PTV with 100% of the dose [4]. Coverage by 100% of the prescription dose is nonstandard.

Impact of posterior axillary boost field on lymphedema

For breast cancer survivors, lymphedema is considered as one of the most important, physically and emotionally, morbidities after surgery, RT, and taxane-based chemotherapy. It has been globally demonstrated that lymphedema has a significant negative impact on patients' QOL [5, 6]. Recently, several studies have been conducted to determine independent predictors of lymphedema after breast RT [15, 16, 21]. A PAB field is considered as a potential RT risk factor for lymphedema. To date, several studies have been conducted to quantify whether the addition of a PAB field can increase the risk of lymphedema, as outlined in Table 2 [10–18].

It has been shown in some studies that patients with a PAB field have an increased risk of lymphedema [11, 12, 14]. Researchers from Massachusetts General Hospital retrospectively evaluated the risk factors of lymphedema in 727 stage I–II breast cancer patients treated with breast conservation therapy [11]. The 10-year actuarial incidence of lymphedema was 4.1%. Their data suggest that regional node irradiation (RNI) is the only significant risk factor for lymphedema, with a 10-year risk of lymphedema from breast-only RT of 1.8% *vs.* 8.9% for RNI (p = *0.001*). In that study, the subgroup receiving a SC field alone (three-field technique) was small. Therefore, these patients were grouped with SC + PAB field patients (four-field technique). Because most patients were treated with the four-field technique, it is difficult to estimate accurately whether the addition of a PAB field increased the risk of lymphedema compared with a SC field alone [11]. A study from of Roswell Park has revealed that the addition of a PAB field increased lymphedema risk [12]. Hinrichs et al. investigated predictors of lymphedema secondary to post-mastectomy RT in 105 patients [12]. They found that the addition of a PAB field doubled the rate of lymphedema from nearly 23% to 47% (p = 0.047). Moreover, their data indicated that RT dose, overlapping the RT technique, RT before 1999, and RT at Roswell Park also were significant predictors of lymphedema. Of note, although SC, internal mammary, mastectomy scar boost, and chest wall tangential photon beam radiation increased the risk of lymphedema, these differences were not statistically significant [12]. In a retrospective study, Bar Ad et al. evaluated the risk factors for progression of lymphedema after breast cancer conversation therapy in 266 stage I-II breast cancer patients at the Hospital of the University of Pennsylvania [14]. The results of univariate Cox models indicated that treatment of the SC nodal region (p = 0.035) and the use of PAB (p = 0.014) were remarkable risk factors for progression of lymphedema. There was no statistically significant difference in arm lymphedema progression between the patients treated with B + SC and B-only (p = 0.4), but patients treated with B + SC + PAB were in greater risk of lymphedema, as compared with patients treated with B-only irradiation (p = 0.01) [14]. The freedom from progression at 5 years of follow-up was 73% for patients treated with B-only irradiation and 36% for patients receiving RT to B + SC + PAB [4].

In contrast, Chua et al. have compared the lymphedema rates between SC-only RT and SC + PAB RT, reporting no significant difference in the rate of lymphedema [10]. From their data it can be seen that the rate of lymphedema was 40% (6 of 15 patients) in the SC field alone, and 31% (42 of 136 patients) in the SC + PAB field group. It should be noted that 10 of 136 patients who experienced severe lymphedema were in the SC + PAB group, no severe lymphedema was found in the SC-only group [10] Hayes et al. quantified well the risk of lymphedema from RNI in a series of 2,579 breast cancer patients [13]. In their study, patients were treated with three different radiation fields setting, 2,169 patients (84%) received radiation to the breast (B), 226 patients (8.8%) to the breast and SC LNs (B + SC), and 184 patients to the breast, SC LNs and a PAB (B + SC + PAB). Overall, lymphedema was observed in 18% of patients at median follow-up of 81 months. The risk of lymphedema was 16%, 23%, and 31% in the B-only, B + SC, and B + SC + PAB group, respectively. The rate of lymphedema in the B + SC + PAB group was comparable with the 47% incidence of lymphedema found by Hinrichs et al. with the addition of a PAB. In addition, the results for the N1 subgroup showed that the adding a PAB over tangents led to an increase in the risk of lymphedema (p = 0.0017), but there was no statistically significant increase in lymphedema risk by adding a PAB to B + SC RT (p = 0.8002). In the N2 subgroup, the addition of a PAB increased the risk of lymphedema 4.5 fold over B + SC RT (p = 0.0011). Meanwhile, there was no statistically significant difference in the breakdown of nodal failures among the three groups (p = 0.35) [13]. Although the study by Hayes et al. had several main strengths, such as the large sample size and the systematic analysis of all potential lymphedema risk factors, retrospective nature of the study and extensive LN dissection or the number of positive LNs can be great risk factors for developing lymphedema owing to the interference of lymphatic drainage irrespective of RT field arrangement.

A study from William Beaumont Hospital evaluated the rates of breast cancer-related lymphedema in 1497 patients treated with whole-breast irradiation [15]. RT parameters were analyzed in patients with and without lymphedema. The data from that study indicated that the addition of regional irradiation (*i.e.,* SC, PAB, and internal mammary field) over whole breast irradiation did not statistically significantly increase the incidence of lymphedema. The findings showed that adding a PAB field approximately doubled the actuarial rate of lymphedema, but it was no statistically significant (14.7% with PAB *vs.* 7.3% without PAB, $p = 0.10$) [15].

Consistent with Hayes et al. study [13], in a prospective single-institution cohort study, Warren et al. determined that the addition of a PAB to SC field did not increase the risk of lymphedema in comparison with SC alone [16]. No statistically significant difference in lymphedema risk between SC and SC + PAB was observed ($p = 0.96$). These findings also were in good agreement with a prior study by Chua et al. [10]. However, Warren et al. found that the addition of RLN radiation, regardless of radiation field type (i.e. SC or SC + PAB), compared with breast/chest wall radiation alone significantly increased the risk of lymphedema with a hazard ratio of 1.7 ($p = 0.025$) [16]. Consistent with Warren et al. study, Graham et al. also reported that using axillary irradiation results in a significant increase in the lymphedema rates whether defined by using a PAB field ($p = 0.004$) or subdivided by any irradiation lateral to the coracoid ($p = 0.002$) [22]. In another report, dosimetric risk factors for the incidence of lymphedema in 172 breast cancer patients treated with RNI radiation at the Massachusetts General Hospital were analyzed [17]. The 2-year cumulative incidence of lymphedema was 22.27% and 20.98% for SC and SC + PAB, respectively. Meanwhile, RLN radiation field type was not associated with the development of lymphedema ($p = 0.66$ for SC *vs.* SC + PAB field). In addition, there was no relationship either between lymphedema risk and other specific RT parameters such as fraction size, extent of humeral head, beam energy, and breast tangent type [17]. It should be noted that the vast majority of patients with lymphedema received axillary LN dissection (87%) [17], a well-documented risk factor for lymphedema development [23]. This, along with a relatively small sample size ($n = 172$) can obscure the impact of the independent RT risk factor on the development of lymphedema.

As reported by Hayes and colleagues, in patients with 4-9 positive LNs (N2 subgroup, $n = 109$) that most often undergo RNI, although the SC field did not increase the risk of lymphedema in comparison with tangents, the use of a PAB field increased lymphedema risk 4.5 fold over tangents and a SC [13]. In this subgroup of patients, this strong correlation resulted in a fall of the number of LNs dissected [13]. As a result, it is necessary to avoid a PAB unless there are absolute indications for its application. It is clear that the rate of nodal recurrence in the PAB group is lower than in the B-only or B + SC group (18/2169 patients in the B group, 8/226 patients in the B + SC group, and 2/184 patients in the B + SC + PAB group) [13]. However, studies have not demonstrated the advantage of a PAB radiation in improving nodal control. Of note, one possible reason for decreasing nodal recurrence in the PAB group may be associated with developed metastatic disease in these patients that results in ceasing time surveillance for nodal recurrences.

As mentioned above, previous reports investigated differences in radiation beam arrangement, *i.e.,* adding a PAB field, but did not clearly determine the volume of axillary tissue irradiated. On the other hand, field designs may be more important for the incidence of lymphedema than field arrangement [18]. A recent study by Gross et al. has documented the relationship between RT field design and lymphedema development [18]. A cohort of 492 patients with stage II-IV breast cancer who had received RLN radiation following breast surgery were divided into three subgroups according to different radiation fields. Group 1 ($n = 101$) received a SC field that excluded the uppermost portion of the level I/II axilla but could include a PAB field, group 2 ($n = 202$) received radiation to the majority of the level I to III of the axilla with or without PAB, and group 3 ($n = 189$) received radiation to the entirety of the anterior and posterior axilla. On the other hand, no patients in group 3 treated were with a PAB field, while more patients in group 2 received a PAB field when compared with group 1, as the control group. The 5-year lymphedema rates in group 2 (37.1%) and group 3 (36.7%) were significantly higher than those in group 1 (7.7%, $p < 0.0001$), despite the fact that more of these patients had undergone sentinel LN biopsy (15–19% *vs.* 6%) when compared with patients in group 1. Of note, the likelihood of the development of lymphedema after sentinel LN biopsy is lower than axillary LN dissection. The incidence of lymphedema at 12 months was 11% after axillary LN dissection and 6% after sentinel LN biopsy in the American College of Surgeons Oncology Group Trial Z0011 [24]. Gross et al. suggest that the lateral border of the 2D nodal RT, as a proxy for the volume of tissue irradiated, is a significant factor for lymphedema development [18]. In other words, radiation of the upper level I to II axilla appears to be particularly important for the development of lymphedema risk after axillary dissection.

As observable in above-mentioned studies, the impact of a PAB RT on the development of lymphedema is controversial. A possible source of these controversies can be the fact that it was unknown what degree of the upper axilla was treated with RNI. As described by Gross et al., radiation field design can result in increasing radiation to the volume of axillary tissues, thereby increasing the incidence of lymphedema [18], whereas other previous studies focused on radiation field arrangement. Besides, a recent study has identified that dose delivered to the axillary-lateral thoracic vessel juncture (ALTJ, the area superior to axillary level I) can be associated with lymphedema risk [25]. As a consequence, radiation field design can be a more relevant risk factor for development of lymphedema than radiation field arrangement. Another issue of possible relevance for the impact of a PAB field on the incidence of lymphedema is the lack of uniformity in measuring lymphedema. As outlined in Table 2, investigators have used multiple metrics to quantify and qualify the incidence of lymphedema, including perometry, arm circumference, *etc*. Therefore, standardizing the method of detecting lymphedema is needed. The testing of the inclusion of upper arm lymphatics in the regional LN irradiation target volume, and universal methodology measuring lymphedema are all areas for possible future studies. Besides, as observable in Table 2, most studies were retrospective and, therefore, may suffer from underestimating actual incidence of lymphedema owing to the lack of documentation in medical record, delayed onset, etc. Moreover, retrospective studies have higher potential sources of bias and confounding. These are issues that will require additional investigation before definitive recommendations can be made regarding the therapeutic index of a PAB radiation.

Conclusion

There are few studies that have investigated whether a PAB is necessary for RLNI. A key factor in using a PAB is the depth of axillary LNs that today is well determined on the basis of CT. The results of this literature review show that depending on dose distribution and patient's anatomy, a PAB field is employed to supplement axillary dose. The PAB field provides a good coverage of level I/II axillary LNs because these LNs are located much deeper. The most important concern regarding a PAB is that it produces a large high-dose region in the AP region of the axilla. To reduce drawbacks of a PAB field RT, physicists and radiation oncologists should optimize and develop a traditional PAB field, as suggested by Jephcott et al. [9] and Hernandez et al. [2]. IMRT technique can also provide excellent dose coverage and simultaneously reduce radiation-induced normal tissue toxicity. However, the use of IMRT techniques involves higher complexity in treatment planning and delivery steps and, therefore, they are not commonly used for the SC and axillary LNs irradiation. Moreover, prospective trials are needed to clarify the efficacy of this approach.

On the one hand, a recent study has suggested that volume and distribution of axillary irradiation may be the most important risk factors of lymphedema development compared with beam arrangement alone. On the other hand, in studies where beam arrangement was investigated, there are conflicting reports on the association of a PAB field with the incidence of lymphedema. Although data reveal that the addition of RNI to breast irradiation significantly increases the risk of lymphedema in patients with breast cancer, prospective studies and the vast majority of retrospective studies have reported the use of a PAB RT does not result in a statistically significant increase in the risk of lymphedema development over SC-alone RT. Of note, there is a trend of increasing risk of lymphedema with a PAB field. Therefore, clinicians should continue to weigh lymphedema risk in individual patients against the benefit of a PAB, in particular after axillary dissection. In the light of these findings, although definitive recommendations regarding the clinical benefit of a PAB field are relatively difficult, axillary radiation with a PAB field is recommended for targeting level I/II axilla if there are clinically matted LNs, ≥ 4 involved axillary LNs, gross extranodal spread of tumor, all LNs dissected positive, positive sentinel LNs without a subsequent completion axillary dissection, an inadequate axillary dissection (< 6 LNs), or the highest LNs dissected being positive [3, 13].

Conflict of interests

The authors declare that they have no conflicts of interest.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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