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Breast surgery and regional anaesthesia

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Regional anaesthesia techniques are an important adjunct to perioperative care of breast surgery patients. This chapter focuses on the practical application, evidence base and advantages of peripheral nerve block regional anaesthesia in the anaesthetic management of patients undergoing breast surgery. Functional anatomy and fascial plane blocks are discussed alongside paravertebral and paraspinal techniques. Guidance on the performance the range of ultrasound-guided blocks is provided. The role that regional anaesthesia may have in reducing the risk of breast cancer recurrence following mastectomy surgery is explored.

Introduction

Breast cancer is the most prevalent cancer in women worldwide, with an estimated 1.7 million women diagnosed annually [1]. With its incidence projected to continue to increase in the UK [1], breast operative procedures are expected to increase correspondingly. The associated surgeries include curative (mastectomies and breast-conserving surgery), diagnostic (axillary lymph node biopsies and clearances) and restorative or other aesthetic procedures.

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Why use regional anaesthesia for breast surgery?

With improved diagnostic techniques and treatment regimens, prognosis in breast cancer is improving, with the 5-year survival of patients diagnosed with primary breast cancer having increased to approximately 85% [2]. The long-term sequelae of those having undergone operative procedures is therefore of ever-increasing importance. Persistent post-surgical pain states in this group is reported in 30–50% [3,4] of patients, up to half of whom may have pain well beyond 5 years [5]. Over one-third of patients who underwent breast cancer surgery have inadequately controlled acute post-operative pain [6]. Inadequate pain management in the post-operative period is an understandable fear for patients; it is additionally burdensome on recovery time, length of stay and overall healthcare cost. The firm association between acute post-operative pain states and chronic post-surgical pain [7] is indeed well validated in those undergoing breast surgery [8]. This condition includes paraesthesia, intercostobrachial neuralgia and phantom breast pain. Whilst disease-specific factors such as extent of surgery and use of radiation are difficult to control, the risk factor of acute post-operative pain [6] is a modifiable target in breast surgery through the use of regional anaesthesia. In this article, we discuss the various regional techniques available to the anaesthetist with an aim to refresh knowledge, consolidate understanding or as a stepping stone to change and develop clinical practice.

Functional anatomy and targets for regional anaesthesia

The innervation of the breast is complex and provides multiple neural targets and interfascial planes through which the delivery of regional anaesthesia can benefit patient care. Its anatomy can be broadly classified by description of its cutaneous/subcutaneous innervation and its muscular innervation.

After exiting the intervertebral foramen, the spinal nerves at the thoracic level divide into their dorsal and ventral rami. The dorsal rami provide innervation to the medial, posterior chest wall and are therefore of little relevance in the scope of breast surgery. The ventral rami, however, run within the paravertebral space and emerge as the intercostal nerves. From here, they travel within the facial plane between the internal intercostal muscle (IICM) and innermost intercostal muscle (IMICM). The lateral cutaneous branch emerges from this facial plane at approximately the mid-axillary line, piercing the internal intercostal, external intercostal and serratus anterior muscles. Upon its division, the lateral cutaneous branch of the intercostal nerve provides innervation to the lateral chest. The anterior cutaneous branch emerges in proximity to the sternum, providing innervation to the medial chest and sternum. The nipple–areola complex has an elaborate and much disputed innervation, and the cranial portion of the breast is likely to derive its innervation in part from supraclavicular nerves. The axilla is supplied predominantly by the intercostobrachial nerve, formed from the lateral cutaneous branch of the T2 ventral rami [9].

The muscular innervation of the breast is derived from the brachial plexus. The lateral pectoral nerve (C5-7) supplies the pectoralis major (upper portion), whilst the medial pectoral nerve (C7-T1) supplies pectoralis minor and major (caudal portion). Both arise from the axilla and travel in pectoral facial planes prior to reaching their point of innervation. The latissimus dorsi muscle is supplied by the thoracodorsal nerve (C6-8), which, upon exit of the posterior wall of the axilla, runs in close proximity to the muscle it innervates. The long thoracic nerve (C5-7) travels along the lateral chest wall superficial to the serratus anterior muscle, for which it supplies [9].

From this description, and a deeper understanding of the relevant anatomy, one can formulate a perioperative analgesic plan according to the anticipated cutaneous/subcutaneous tissue disruption. Fig. 1 can be used as a reference for proposed anatomical targets of the regional anaesthesia techniques discussed during this article.

Rationale for the decline in popularity of thoracic epidurals

The use of thoracic epidural analgesia (TEA) has been a long-established means of delivering perioperative anaesthesia and analgesia for major breast surgery operations. These authors experience that patients are rarely in favour of the technique, with health beliefs that focus heavily on the dangers.

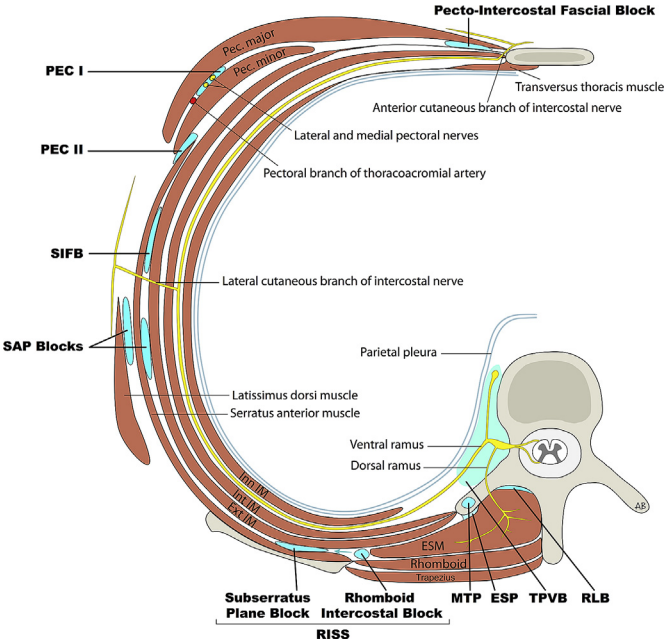

Fig. 1. Schematic diagram of anatomy and injection sites for regional anaesthesia targets in breast surgery. Transverse section at the level of T3. Ext IM (external intercostal muscle), Int IM (internal intercostal muscle), Inn IM (innermost intercostal muscle), ESM (erector spinae muscle), RLB (retrolaminar block), TPVB (thoracic paravertebral block), ESP (erector spinae plane block), MTP (Mid-point transverse process to pleura block), SAP (serratus anterior plane), SIFB (serratus intercostal fascial block). Image appears courtesy of Dr Ann Barron.

The risks of TEA are well investigated [10], with immediate complications including dural-puncture, high or total spinal and local anaesthetic toxicity (LAST). Use of ultrasound can improve both accuracy of needle placement and outcome [11,12], but TEA failure rate remains high [13], and hence, it has been largely superseded by other techniques. Whilst it may still have a role in prolonged flap reconstructions (transverse rectus abdominis muscle (TRAM)/deep inferior epigastric perforator (DEIP)/latissimus dorsi (LD) or bilateral surgery, TEA is declining in popularity as a standard technique for perioperative analgesia [14].

In contrast to the TEA, the paravertebral block (PVB) provides unilateral spread. It is from this characteristic difference that it is thought to display its more favourable side effect profile of fewer pulmonary complications and less hypotension [15]. In a Cochrane review of TEA in comparison to PVB for patients undergoing thoracotomy, there was moderate-quality evidence that PVB resulted in fewer minor complications (including hypotension, nausea and vomiting and urinary retention) whilst maintaining matched efficacy for post-operative pain [16]. This demonstrable reduction in sympathectomy makes it additionally more suitable in the day surgery unit setting, when compared to TEA.

Thoracic paravertebral block

The thoracic paravertebral block was first performed by Hugo Sellheim of Leipzig in 1905 to achieve analgesia and muscle relaxation in abdominal surgery [17]. Its use diversified and multiplied, reaching a peak of publications and descriptions in 1920–1930s from which point its use apparently declined [17]. In more recent times, the technique has had resurgence and has now become an established staple of regional anaesthesia for breast surgery, for which it is well validated to provide excellent analgesia and a low risk of adverse events. A recent meta-analysis of 15 randomised trials demonstrated superior pain scores following PVB when compared with opioids at all time periods up to 48 h following surgery,

with most of the studies including patients undergoing minor and major elective breast tumour resection or mastectomy [18]. In patients undergoing breast surgery, the PVB confers additional benefits of reduced post-operative nausea and vomiting and length of stay [9]. There is limited evidence of a reduction in chronic post-surgical pain at 6 and 12 month follow-up [19], although meta-analysis of three trials including chronic pain outcomes demonstrated high heterogeneity ($I^2 = 53\%$) and no significant difference for risk of chronic pain at 6 months following breast surgery (RR: 0.16; 95% CI: 0.02–1.13; $p = 0.07$) [18].

The paravertebral space (PVS) is classically described as a triangular-shaped area bounded medially by the vertebral bodies, intervertebral discs and intervertebral foramina; anteriorly by the parietal pleura and posteriorly by the superior costotransverse ligaments, ribs and transverse processes [20]. Its content includes the spinal (intercostal) nerve, its dorsal ramus, rami communicates and the sympathetic chain [17].

The classical landmark-based technique for PVB is described as perpendicular advancement of the needle 2.5–3 cm lateral to the most cephalad aspect of the spinous process. Upon contact of the transverse process, the needle is walked off the bone, above or below, until a loss of resistance to the constant pressure of a column of saline or air is observed [21].

Use of high-frequency ultrasound for accurate needle placement within the paravertebral space has gained popularity during the last decade. There are numerous descriptions and approaches to the US-guided PVB in the literature. These descriptions can be broadly classified, by probe position relative to the thorax, as transverse [22–24] or paramedian sagittal [25] using either an in-plane [23–25] or out-of-plane technique [22], with varying ultrasound probe positions and angulations. Both techniques are summarised in sections A and B of Fig. 2. The PVB can be sited at a single level, multiple levels or be prolonged by the placement of a catheter. There are no dosing-finding studies for PVB in breast surgery, with a single randomised trial reporting similar segmental spread of sensory block produced by continuous thoracic paravertebral block irrespective of whether 0.2% or 0.5% ropivacaine was infused [26]. A single trial demonstrated that dermatomal sensory block spread was not significantly different in patients randomly allocated to a single or 5 level injections of an equal volume of PVB injectate (25 ml of 0.5% ropivacaine). As single injections are more efficient and present fewer risks to patients, they may be justified for surgery where extensive dermatomal spread is not required [27].

		Cutaneous & Subcutaneous innervation				Muscle innervation			
		Intercostal nerves			Cervical plexus	Brachial plexus			
	Nerves	Lateral cutaneous branches	Anterior cutaneous branches	Intercostobrachial nerve	Supraclavicular nerves	Lateral pectoral nerves	Medial pectoral nerves	Thoracodorsal nerve	Long Thoracic nerve
	Innervation of:	Lateral breast	Medial breast	Axilla & medial upper arm	Cranial breast	Pectoralis major	Pectoralis minor & major	Latissimus dorsi	Serratus anterior
Regional anaesthesia technique	Thoracic epidural	☑	☑	☑	X	X	X	X	X
	Paravertebral block	☑	☑	☑	X	X	X	X	X
	PECS 1 Block	X	X	X	X	☑	☑	X	X
	PECS 2 Block	☑	X	☑	X	☑	☑	☑	☑
	Serratus	☑	X	☑	X	X	X	☑	☑
	PIFB	X	☑	X	X	X	X	X	X
	SIFB	☑	X	☑	X	X	X	X	?
	RISS	☑	X	X	X	X	X	X	X
	ESP	☑	?	X	X	X	X	X	X
	RLB	?	?	X	X	X	X	X	X
	MTP	☑	☑	X	X	X	X	X	X

Fig. 2. Anatomical targets of regional anaesthesia. Green (Tick): proven coverage. Orange (question mark): unknown or unproven. Red (cross): does not cover.

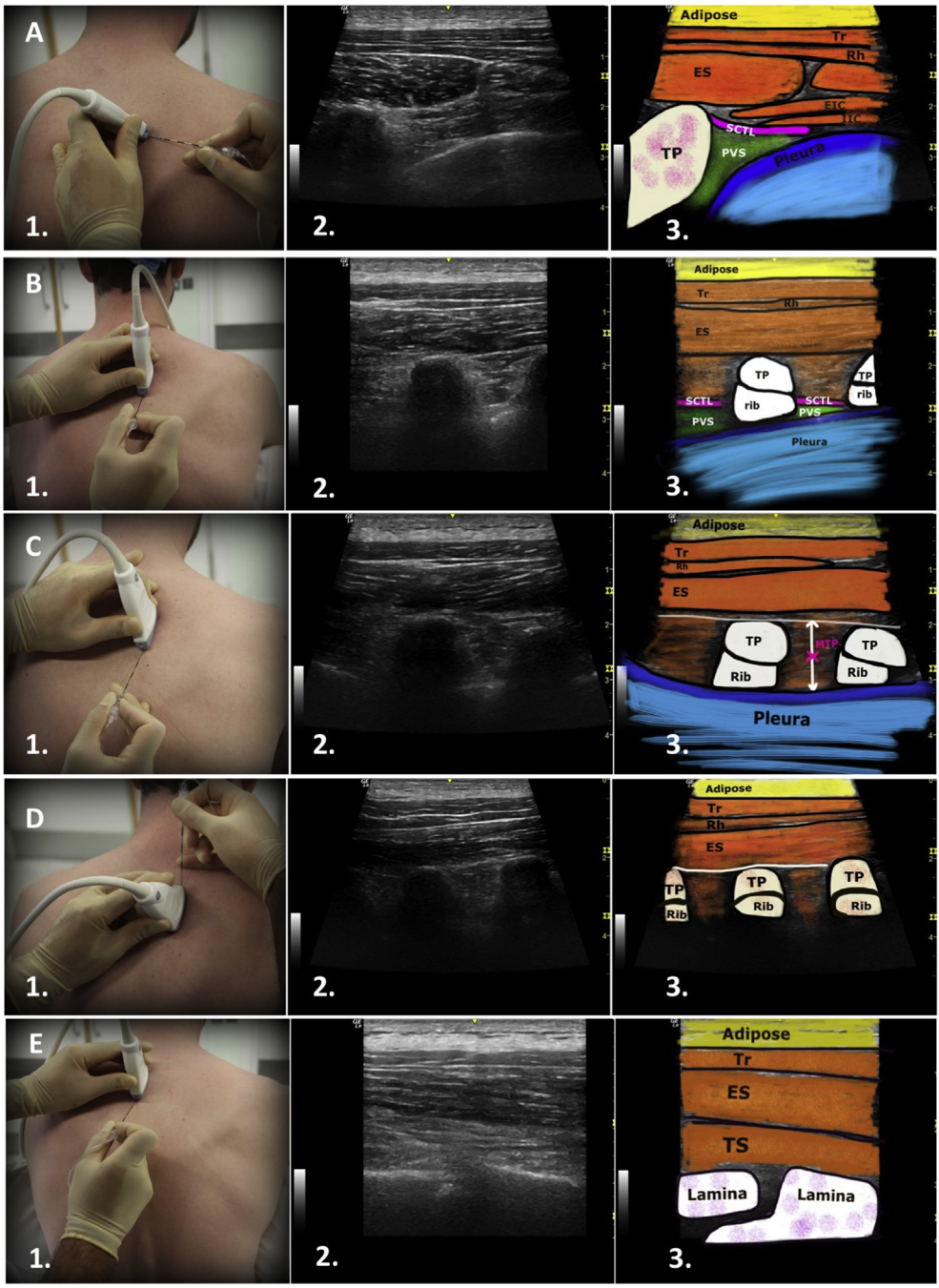

Fig. 3. Summary of ultrasound probe position, imaging and anatomical structures for paravertebral, MTP, ESP and retrolaminar blocks. Letters relate to block technique (A to E). 1: patient, probe and needle position. 2: ultrasound image generated. 3: overlay of structures. A: Transverse In-Plane PVB. B: Paramedian Sagittal PVB. C: Mid-point transverse process to pleura (MTP) block. D: Erector Spinae Plane (ESP) block. E: Retrolaminar Block. Tr (Trapezius muscle); Rh (Rhomboid muscle); ES (erector spinae muscle complex); EIC (external intercostal muscle); IIC (internal intercostal muscle); SCTL (Superior costotransverse ligament); TP (transverse process); PVS (Paravertebral space); TS (transversospinalis muscle).

Paramedian sagittal approach to the paravertebral block

With the patient positioned in the sitting, lateral or prone position, a high-frequency linear probe is placed in a paramedian orientation over the lateral ribs, as shown in section B1 of Fig. 3. The superficial trapezius and rhomboid muscles are visualised with the hyperechoic rib edges beneath. Between them, the external intercostal muscle (EICM), internal intercostal muscle (IICM) and innermost intercostal muscle (IMICM) may be seen, with the 'comet tail' appearance of the pleura below. The probe is then moved medially towards the costotransverse junction where the hyperechoic rims of the ribs become replaced by the transverse processes, which are more superficial and have a flattened 'tomb stone'-like appearance. The erector spinae (ES) muscle complex becomes visible deep to rhomboid at this more medial probe position. At this point, the superior costotransverse ligament (SCTL) will be visualised, and with lateral angulation of the ultrasound beam, the pleura may equally be brought into view. It is our practice to rotate the caudad pole of the probe slightly away from the midline to best facilitate in-plane needling. The block needle is then advanced in a caudad to cephalad direction to traverse the SCTL. A test-dose of LA is instilled to witness the pleural drop as a safety end-point prior to further administration of LA.

Transverse approach to the paravertebral block

Typically described in the lateral-decubitus or prone positions, a high-frequency linear probe is placed on the rib of desired block level, with the medial edge of the probe in contact with the spinous process. This approach is summarised in section A of Fig. 3. The long-axis of the rib is visualised with its hyper-echoic periosteum and drop-away artefact below, and the probe is then moved caudally to visualise the musculature of the intercostal space with the characteristic pleura below. The hypo-echoic appearance of the paravertebral space is found to contrast with the hyper-echoic inferior part of the transverse process medially and the pleura inferiorly. Hydro-dissection may aid in identification of the internal and innermost intercostal muscles that bound it superiorly. The needle is passed, in-plane, to traverse the SCTL (indistinguishable from the internal intercostal ligament at this point [24]). Negative aspiration and ventral movement of the pleura upon injection of LA aid in confirmation of needle placement within the paravertebral space. There is currently no evidence of superiority of one ultrasound-guided block technique over another.

Older studies, from a landmark-based technique, demonstrated complications with PVB that included pneumothorax (0.5%) [28]. Pace et al. retrospectively reviewed complications from 1427 single-injection, transverse, in-plane ultrasound-guided paravertebral blocks. They reported only 6 complications (0.7%), including hypotension and symptomatic bradycardia [29], with similar results replicated by a systematic review [30]. This can be viewed as encouraging for the added safety that an ultrasound-guided technique brings to the paravertebral block.

Fascial plane blocks

Pectoral blocks (Pecs-1 and Pecs-2)

Pectoral (Pecs) blocks are superficial interfascial plane blocks that grant access to the branches of the brachial plexus that supply the pectoral muscles and upper anterior thoracic wall [31]. Injection of LA is made with the intention of encouraging LA spread, and therefore, coverage of desired nerves, without precise needle localisation to individual nerves, is required. The principal nerves involved are the lateral pectoral nerve (LPN) and medial pectoral nerve (MPN). LPN runs deep into the inner surface of pectoralis major muscles and innervates the clavicle, shoulder joint and costoclavicular ligaments. MPN is located deep into pectoralis minor muscle, to which it supplies motor and sensory innervation. MPN also supplies the ventral aspect of the chest and, in conjunction with the intercostobrachial nerve, the chest wall medial to the axilla.

Pecs-1 blocks aim to block both LPN and MPN. First described by Blanco in 2011 [32], the technique involves injecting LA in the fascial plane between pectoralis major and minor muscles. The block is best

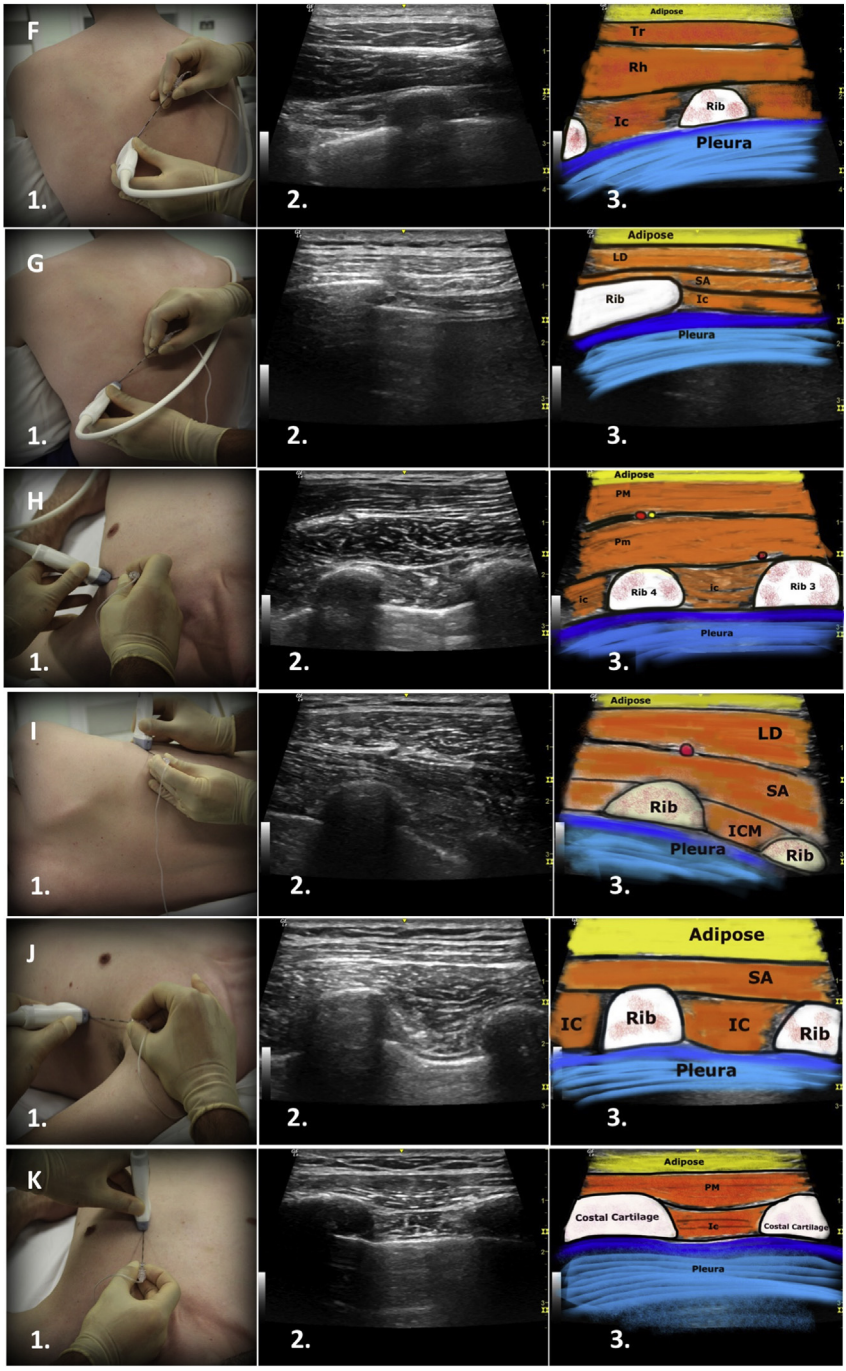

Fig. 4. Summary of ultrasound probe position, imaging and anatomical structures for RISS, PECS, SAP, SIFB and PIFB blocks. Letters relate to block technique (F to K). 1: patient, probe and needle position. 2: ultrasound image generated. 3: overlay of structures. F: Rhomboid Intercostal part of RISS block. G: Sub-serratus part of RISS block. H: PECS block. I: Serratus Anterior plane block (SAP). J: Serratus Intercostal fascial Block (SIFB). K: Pectointercostal fascial block (PIFB). Tr (Trapezius muscle); Rh (Rhomboid muscle); Ic (intercostal muscle); LD (Lattisimus dorsi muscle); SA (serratus anterior muscle); PM (Pectoralis major muscle); Pm (Pectoralis minor muscle); ICM (intercostal muscles).

performed with the patient supine, either with the arm next to the chest or abducted 90°. Needle injection should occur adjacent to the pectoral branch of the thoracoacromial artery. It should be done with the US probe in the paramedian sagittal plane on the coracoid process, as shown in section H of Fig. 4. Slight rotation allows the artery to be visualised and in-plane needling to be accomplished. The needle can then be inserted, followed by hydrodissection of the fascial plane beneath pectoralis major confirming correct localisation. There are no dose-finding studies for Pecs-1 blocks, but an injectate volume of approximately 0.2–0.4 ml/kg provides appropriate coverage.

Pecs-2 blocks additionally block the lateral rami of intercostal nerves and the long thoracic nerve. Strictly speaking, a Pecs-2 block consists of a Pec-1 injection, plus a second injection made under pectoralis minor muscle in the anterior axillary line at the level of the fourth rib. Again, 0.2–0.4 ml/kg of long-acting LA is recommended. A catheter can be introduced into both fascial plane insertion sites, for prolonged post-operative analgesia. Analgesic equivalence of nerve blocks clearly depends on surgical and technical performance factors, but a single, small randomised trial demonstrated that Pecs-2 block can provide superior postoperative analgesia following radical mastectomy than PVB [33]. A combination of PVB with Pecs-2 block can be sufficient to facilitate breast cancer surgery, including mastectomy, with sedation rather than general anaesthesia [34].

Because of superior axillary coverage, the Pecs-2 block is better suited to breast surgery with axillary node dissections, whilst Pecs-1 is suited for lumpectomy and prosthesis surgeries.

No serious complications have been reported after US-guided Pecs blocks, although the needling approach means that pneumothorax and vascular injury to the pectoral branch of the thoracoacromial artery may occur.

Serratus anterior plane block (SAP)

The serratus anterior plane block (SAP) provides anterolateral and partial posterior thoracic wall analgesia, affecting dermatomes from T2 to T9. SAP is essentially a variation on the Pecs-2 block, affecting predominantly the lateral cutaneous branches of the thoracic intercostal nerves, along with intercostobrachial, thoracodorsal and long thoracic nerves [35]. The block is performed further posteriorly and caudally than Pecs-2, where the target nerves are located between the serratus anterior and the latissimus dorsi muscles.

The patient's arm should be brought forward or elevated to allow access to the axilla. The US probe should begin in a similar position for Pecs-2, at the mid-axillary line (section I of Fig. 4). Sliding the probe caudally allows the serratus anterior muscle to be identified above the ribs. Once the fourth and fifth ribs are visible, the probe should be tilted posteriorly until the thicker latissimus dorsi muscle can be seen over overlying the thinner, deeper serratus anterior muscle. Alternatively, the patient can be placed in the lateral position to aid scanning of the lateral aspect of the thorax and needle insertion. Injection should be made, in plane, with 0.4 ml/kg LA, keeping the ribs and pleura in view. The needle endpoint is either in the fascial plane between latissimus dorsi and serratus anterior (taking care to avoid the thoracodorsal artery) or below serratus anterior between it and the rib below. There is no clear clinical evidence to distinguish whether superficial or deeper deposition of LA is preferable [36] in breast surgery. Although the original cadaveric study indicated wider dermatomal spread from T2 to T9 with superficial injections [33], a more recent and larger study has shown that high-volume injectate spread provides consistent coverage irrespective of plane of injection relative to serratus anterior muscle [37].

SAP has been used for rib fractures [38], thoracotomies [39], and shoulder surgery [40], alongside reconstructive breast surgery [41].

No serious complications have been reported, but the block requires more advanced needling skills than Pecs-2 and, being in close proximity to the pleura, pneumothorax is a risk.

Pecto-intercostal fascial block (PIFB)

The PIFB provides analgesia to the anterior thoracic wall, by blocking anterior cutaneous branches of intercostal nerves [42]. LA is injected lateral to the sternum between the pectoralis major muscle and external intercostal muscle. PIFB is one of the two interfascial techniques described to provide

analgesia to the medial chest and breast, the other being the transversus thoracis muscle plane block [43]. It is the opinion of the authors that the PIFB is the safer technique because of its increased distance from both the pleura and the internal thoracic vessels.

Lateral to the sternum, the short axis of the costal cartilages and associated ribs are identified with a probe in the sagittal plane (section K of Fig. 4). The external intercostal muscle can be seen between ribs, overlain by pectoralis major. In the same plane, a needle should be advanced until the fascial plane between muscles is located at the tip, at the mid-point between ribs. Approximately 2–3 ml of injectate will provide sufficient LA to provide analgesia to the local dermatome. Larger volume will spread in the fascial plane to block the multiple levels of the cutaneous branches of intercostal nerves.

The main potential roles for PIFB in breast surgery are to supplement a lateral interfascial plane block such as PECS, SAP or the Serratus intercostal fascial block (SIFB). There are no randomised studies of PIFB, and few case studies have been reported, but the block may be useful as an equivalent to intercostal nerve block in breast surgery [44]. No serious complications have been reported.

Serratus intercostal fascial block (SIFB)

The SIFB is a lateral block equivalent to the PIFB, which targets the lateral cutaneous branches of intercostal nerves [42].

The ultrasound probe is positioned in the axillary midline, in the sagittal plane (section J of Fig. 4). The intercostal space between the fourth and fifth ribs is identified, and the needle tip is positioned below the serratus anterior muscle and above the external intercostal muscle. Similar volumes of LA to the PIFB will produce similar anatomical coverage of analgesia.

Given the localised nature of PIFB and SIFB, provision of both blocks together is necessary to provide sufficient hemithoracic analgesia for mastectomy. No serious complications have been reported.

Rhomboid intercostal and subserratus plane block (RISS)

The RISS tissue plane extends deep into the erector spinae muscle medially and deep into the serratus anterior muscle laterally. Unlike the fascial plane blocks described above, the RISS block is performed posteriorly and captures the lateral cutaneous branches of the thoracic intercostal nerves earlier in their anatomical course [45].

With the patient in a lateral decubitus position, the US probe is placed in the sagittal plane, medial to the medial border of the scapula, as shown in section F of Fig. 4. The cranial end of the probe is then rotated slightly medially, so that the short axis of the fifth and sixth ribs can be seen below the trapezius and rhomboid major muscles. The probe can be slid cranially or caudally depending on the desired dermatomal coverage. Five to 10 mL of LA should be injected between the rhomboid major muscle and deeper external intercostal muscle. This represents the first of two injection points. The second injection point involves placement of the needle tip into the subserratus plane. The US probe should be moved caudally and laterally, until just caudal to the angle of the scapula. The same needle entry point can be retained, with the needle re-angled, or, if necessary, the needle can be re-inserted. The needle tip should be advanced to track deeper, ending below the serratus muscle and in plane with the US probe. Twenty millilitres of LA should be injected.

As the newest of the chest wall fascial plane blocks, there are very limited clinical validation studies. A single retrospective case series demonstrated block efficacy and dermatomal sensory loss for patients with a variety of clinical indications including upper abdominal surgery, lung transplant, rib fracture and cancer pain [45]. No breast surgery patients were included in the case series, but the sensory loss described would be sufficient for breast surgery, extending almost to the midline medially and laterally to the axilla. No complications were reported in the only case series of 15 patients.

Paraspinal plane blocks

The classically described paravertebral space is bordered posteriorly by a ligamentous complex that includes the SCTL. Conventional thinking would have it that successful PVB would require access to the paravertebral space, through this complex, with the operator's block needle. Prior to the

advent of dynamic ultrasound-guided techniques for paravertebral block, one could only suppose needle location. Discussion in recent literature has highlighted how ultrasound imaging and simple geometry would suggest a classically described PVB (with advancement 1 cm cephalad/caudad after contacting the transverse process) would not guarantee a needle tip placed anterior to the superior costotransverse ligament. It is therefore suggested that many PVBs are indeed PVBs 'by proxy' [20]. Evidence of this is given by the observed cadaveric spread of methylene blue injected posterior to the superior costotransverse ligament (and therefore by definition outside the paravertebral space) found within the sympathetic chains and intercostal nerve routes within the paravertebral space [46]. It is through this indirect spread that the proposed, most recently described, paraspinal plane blocks are likely to act.

Erector spinae plane (ESP) block

This technique was first described in an outpatient setting as a novel technique to effectively manage thoracic wall neuropathic pain [47]. With the patient sitting, a high-frequency linear ultrasound probe is placed in the paramedial sagittal orientation anatomically 3 cm lateral to the T5 spinous process (section D of Fig. 3). The muscles of (superficial to deep) trapezius, rhomboid and erector spinae are visualised, with the hyper-echoic transverse process beneath. Using an in-plane cephalad to caudad technique, the operator advances their needle through erector spinae towards the transverse process. Upon contact, hydro-dissection is used to open up the erector spinae plane (deep into the muscle) for LA delivery. A volume of 20 ml LA is sufficient to provide analgesic coverage for breast surgery [47].

Since its early description, there have been published reports of its use in adults and paediatrics and in surgeries ranging from chest wall, thoracic, abdominal and orthopaedic lower limb [48]. In the first review of published evidence, of the 242 cases described, the majority were single shot and thoracic. There was reported reduction in opiate requirement and objective reduction in nerve conduction, with only a single adverse outcome of pneumothorax [48]. Although encouraging, these results highlight the need for clinical trials to properly evaluate this new technique's effectiveness.

Retrolaminar block

The retrolaminar block was first described as a landmark technique that was effective in reducing perioperative opiate requirements in breast surgery [49,50]. In 2013, the technique was adapted for use with ultrasound [51,52]. With the patient sitting, a high-frequency linear ultrasound probe is placed in the paramedial sagittal orientation at mid-thoracic level and moved from medial to lateral (section E of Fig. 3). The hyperechoic laminae and transverse process are identified, with the muscle groups superficial to them. Using an in-plane technique, and needle movement from cephalad to caudad, the operator aims to contact the lamina, passing deep into the bulkier erector spinae muscle. Following negative aspiration, instillation of injectate opens up the retrolaminar space, allowing insertion of a catheter if so required.

Whilst the technique has shown promise in opiate-sparing bilateral mastectomy surgery [51], this benefit was not conferred when compared against PVB in RCT studying radical mastectomy [53].

Mid-point transverse process to pleura (MTP) block

The ultrasound-guided Mid-point Transverse process to Pleura (MTP) block is one of the more recently described paraspinal techniques [54]. With the high-frequency ultrasound probe held in a parasagittal orientation, the operator adjusts angulation until the tips of the transverse processes and pleura are seen within the same image (as described for parasagittal PVB). In-plane needling is from caudad to cephalad, with an aim not to traverse the SCTL but to place to tip of the block needle at the mid-point between the transverse process and pleura (section C of Fig. 3). This end-point has the advantage of keeping the block needle away from both neural tissue and the pleura. Cadaveric analysis of multilevel injections using this technique demonstrated spread of injectate was achieved to the paravertebral space at the injection level and frequently to adjacent levels too. This was correlated

clinically by a series of two patients successfully receiving opiate-sparing breast surgery using an MTP technique [54].

Cancer recurrence

Decision-making regarding regional anaesthesia for specific surgical procedures is often swayed by patient factors and evidence on proximate benefits such as superior analgesia, reduced opioid requirements and avoiding general anaesthesia. Research exploring such proximate outcomes is important but fails to address questions on potentially more meaningful longer term benefits. Evidence that regional anaesthesia may reduce breast cancer metastasis and recurrence is theoretically plausible and would have profound implications for anaesthetists and oncological surgeons alike, changing the way that anaesthetic technique is integrated within perioperative care.

Metastatic cancer recurrence is a far more common cause of death in breast cancer patients than direct mortality due to the primary tumour. Death due to metastatic disease is estimated to occur in 30%–40% of patients, despite surgical resection, chemotherapy and radiotherapy [55]. Recurrence following breast cancer treatment has a complex aetiology, but increasing evidence indicates that factors within the perioperative period for surgical resection, including regional anaesthesia techniques, may influence the metastatic potential of cancer cells.

Cancer metastasis involves the release and migration of tumour cells from a source site, after which they must evade the host immune surveillance response and re-establish disease at a distant location. Surgical manipulation may paradoxically promote metastasis by liberating micro-deposits of tumour during resection [56] and triggering an immunological and hormonal stress response that impairs physiological defence mechanisms against metastasis [57]. Natural killer (NK) cell detection and elimination of circulating metastatic cell forms represent the most important immune protection against recurrence, an innate mechanism that is recognised to be impaired during surgical stress [58]. NK cell function is correlated with susceptibility to multiple forms of cancer [59], and surgery is associated with both decreased NK cell activity and increased metastasis. Such effects that can be reversed by blocking inflammatory responses in animal models of cancer [58].

Microscopic residual disease, despite extensive marginal resection, is recognised as an independent risk factor for cancer recurrence. Circulating breast tumour cells may be present for many years after mastectomy without macroscopic evidence of disease recurrence [60], with cellular dormancy states representing a mechanism for recurrence after prolonged disease-free intervals. As there is no surgical technique for guaranteeing that cellular residuals are not dispersed during resection, promotion of favourable balance between immune factors that protect against cellular metastasis of a breast cancer during the perioperative period represents an important strategy for enhancing clearance.

Regional anaesthesia has the potential to dramatically reduce pain and therefore the inflammatory stress response to surgical tissue trauma. Studies of inflammatory milieu in breast cancer patients have been favourable. Women undergoing primary breast cancer resection receiving PVB have reduced post-operative concentrations of pro-inflammatory cytokines including IL-1β and increased concentrations of anti-inflammatory cytokines, such as IL-10 [61]. In addition, the serum of women receiving PVB and propofol total intravenous anaesthesia exhibited greater NK monocyte activity than those receiving sevoflurance with opioids [62]. Regional anaesthesia reduces opioid use, a class of analgesics with known direct effects on breast cancer cellular function [63]. However, there is conflicting overall evidence on whether opioids are beneficial or harmful in contributing to cancer spread [64,65].

One of the first clinical studies to investigate the specific question of whether regional anaesthesia could influence breast cancer recurrence was a retrospective review of 129 patients undergoing mastectomy with axillary dissection [66]. Fifty patients who received general anaesthesia and PVB with catheter infusions for 48 h post-operatively were matched against 79 patients with similar characteristics, tumour staging and prognostic factors, but they received general anaesthesia and morphine only for surgery. Recurrence and metastasis-free survival at 36 months were significantly higher, at 94% (95% CI 87–100%), in the PVB group compared with that at 77% (95% CI 68–87%) in the morphine group. These dramatic findings, offering a hint at a revolutionary re-framing of anaesthetic technique, need to be interpreted within the context of the study type: a retrospective study with inherent risk of bias.

Two more recent meta-analyses of regional anaesthesia and patient outcomes, covering studies with all cancers and nerve block techniques, failed to show any evidence of reduced cancer recurrence in patients receiving regional anaesthesia [67,68]. More specifically, this negative finding has now been replicated in a systematic review [69], including four retrospective studies in breast cancer patients receiving either PVB or epidural anaesthesia [70–74] and one hugely underpowered randomised pilot study [75]. The largest of these studies [70] included a median follow-up of 5.5 years in 1107 breast cancer patients after primary surgery and showed no significant outcome differences between regional anaesthesia and general anaesthesia for overall survival, disease-free survival or local regional recurrence. No studies, to date, have investigated fascial plane blocks in breast cancer surgery.

Bias in retrospective studies is a serious problem when interpreting validity. In the retrospective studies of regional anaesthetic technique and cancer outcomes, treatment allocation is unwittingly influenced by anaesthetist and patient factors. For example, patients with extensive metastasis, recurrent or bilateral tumour may be less likely to receive PVB. In this manner, outcome is predictive of intervention, rather than the converse. Likewise, the effect of surgical operator or baseline predictors of cancer recurrence factors is not easily measured and controlled for. Propensity score matching techniques can help, by accounting for a variable's influence on outcome or the likelihood a subject will receive treatment [76], but no large propensity score studies of regional anaesthesia have yet been conducted in breast cancer patients.

Clearly, what is needed is a large, multicentre randomised trial of regional anaesthesia and breast cancer outcomes. Such an international trial is currently underway, involving patients with stage 1–3 breast cancer undergoing mastectomy with or without axillary dissection (NCT00418457) [77]. Upon close of recruitment, over 1300 patients will have been randomised to regional anaesthesia (thoracic epidural or PVB) with propofol sedation or sevoflurane and postoperative morphine patient-controlled analgesia, then followed for up to 10 years after surgery to evaluate cancer recurrence and metastasis. Although the trial commenced in 2007, no clinical outcomes have been published yet. Enrolment has been extended, as fewer cancer recurrences than anticipated have been detected, but the study is finally approaching completion, expected in 2019.

Standard of practice in anaesthetic technique for breast cancer has the potential to be profoundly influenced by studies of metastatic recurrence. Whilst laboratory studies of have shown that regional anaesthesia attenuates perioperative immunosuppression with mechanistic links to tumour metastasis, retrospective clinical studies have not consistently demonstrated translational evidence of improved survival. A well-planned prospective randomised trial is promising results within the near future and is expected to help verify the plausible benefits of regional anaesthesia technique on breast cancer outcomes. For the time being, a decision to provide a patient with regional anaesthesia for breast surgery should still be determined by patient and proximal factors, with insufficient evidence to justify widespread provision on oncological prognostic grounds.

Summary

Surgery on the breast covers a range of diagnostic, therapeutic and cosmetic procedures. A significant proportion of patients suffer significant acute post-operative pain, some of whom progress to develop persistent post-surgical pain. Regional anaesthesia of the breast is therefore an important area of practice, made more challenging by the complex nature of the innervation of the area.

Thoracic epidural analgesia has largely been superseded by PVB as the mainstay for breast analgesia and a significant evidence base of benefits for PVB exists. However, despite ultrasound guidance, there is a general reluctance of practitioners to perform PVBs. This has paved the way for descriptions of new paraspinal plane and interfascial plane blocks, which bring with them the potential for analgesic benefit without the risk of PVB. In many instances, these claims remain to be validated.

A fundamental difference between PVBs and fascial plane blocks for breast surgery is that only PVBs currently have evidence for attenuation of the surgical stress inflammatory response. In theory, this mechanistic distinction opens the potential for PVBs to avoid the spinal hypersensitisation and alteration to normal patterns of nociceptive neuron stimulation induced by tissue damage. Downstream consequences of these effects may be superior long-term pain benefits, which is particularly pertinent given the high incidence of chronic pain states following breast cancer surgery. Limited evidence from

clinical trials reveals that PVBs may not reduce the relative risk of chronic pain but may reduce chronic pain intensity. There is no equivalent evidence base for fascial plane blocks.

Likewise, comparative studies of clinical efficacy between fascial plane blocks and PVBs are also currently very limited. A combination of two (or more) techniques may provide the optimal solution for perioperative analgesia in breast surgery, with a PVB component providing stress response suppression and fascial plane block enhancing specific analgesic coverage. Clinical trials are still required to answer such questions.

There is potential for regional anaesthesia of the breast to have long-term benefits on cancer recurrence, and this is the subject of much anticipated research currently being undertaken.

Practice points

- Breast cancer is the most prevalent cancer in women worldwide, presenting an important challenge to establish optimal anaesthetic management for patients during cancer excision or cosmetic restoration surgery.
- Newer regional anaesthesia techniques, such as fascial plane blocks and paravertebral nerve blocks, have superseded traditional thoracic epidurals by offering comparable analgesia but with lower risk of complications.
- Use of ultrasound during provision of regional anaesthesia has improved both efficacy and safety. Ultrasound-guided paravertebral blocks may confer longer term benefits for breast cancer patients by reducing the risk of chronic pain.
- PECS, like other fascial plane blocks for breast surgery, may be more suitable for day-case procedures, as there is no risk of inadvertent neuraxial blockade.
- Laboratory and in vitro studies support the hypothesis that regional anaesthesia during breast cancer excision may reduce the incidence of cancer recurrence. Clinical studies, however, have yet to provide clear corroboration.

Research agenda

- The comparative value of fascial plane nerve blocks of the thoracic wall requires further investigation against the standard of analgesia provided by PVBs.
- Evidence of PVB single injection versus continuous infusion is required as are studies randomising regional anaesthesia techniques against local infiltration and wound catheter (rather than nerve block catheter) infusions.
- Objective investigations of the anaesthetic benefits of combinations of fascial plane and PVB are needed to provide clearer options for patients wanting to avoid general anaesthesia for breast surgery.
- Studies that report outcomes of pain on movement or chronic postmastectomy pain syndrome are still required.
- Evidence of longer term benefits, including functional outcomes such as chronic pain and cancer recurrence, is warranted for regional anaesthesia and breast surgery.
- A large randomised controlled trial is due to complete in 2019, which will provide evidence on vital clinical outcomes of breast cancer recurrence in patients receiving regional anaesthesia during mastectomy.

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References

[1] Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. [Accessed 20 October 2018].
[2] Mouridsen HT, Bjerre KD, Christiansen P, et al. Improvement of prognosis in breast cancer in Denmark 1977–2006, based on the nationwide reporting to the DBCG Registry. Acta Oncol 2008;47:525–36.
[3] Jung BF, Ahrendt GM, Oaklander AL, et al. Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain 2003;104:1–13.
[4] Gartner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009;302:1985–92.
[5] Macdonald L, Bruce J, Scott NW, et al. Long-term follow-up of breast cancer survivors with post-mastectomy pain syndrome. Br J Cancer 2005;92:225–30.
[6] Poleshuck EL, Katz J, Andrus CH, et al. Risk factors for chronic pain following breast cancer surgery: a prospective study. J Pain 2006;7:626–34.
[7] Macrae WA. Chronic pain after surgery. Br J Anaesth 2001;87:88–98.
[8] Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain 2011;12:725–46.
[9] Woodworth GE, Ivie RMJ, Nelson SM, et al. Perioperative breast analgesia: a qualitative review of anatomy and regional techniques. Reg Anesth Pain Med 2017;42:609–31.
[10] Cook TM, Counsell D, Wildsmith JA, et al. Major complications of central neuraxial block: report on the third national audit project of the royal college of anaesthetists. Br J Anaesth 2009;102:179–90.
[11] Kessler J, Moriggl B, Grau T. The use of ultrasound improves the accuracy of epidural needle placement in cadavers. Surg Radiol Anat 2014;36:695–703.
[12] Auyong DB, Hostetter L, Yuan SC, et al. Evaluation of ultrasound-assisted thoracic epidural placement in patients undergoing upper abdominal and thoracic surgery: a randomized, double-blind study. Reg Anesth Pain Med 2017;42:204–9.
[13] Ready LB. Acute pain: lessons learned from 25,000 patients. Reg Anesth Pain Med 1999;24:499–505.
[14] Rawal N. Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med 2012;37:310–7.
*[15] Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy–a systematic review and meta-analysis of randomized trials. Br J Anaesth 2006;96:418–26.
[16] Yeung JH, Gates S, Naidu BV, et al. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev 2016;2:CD009121.
[17] Richardson J, Lonnqvist PA. Thoracic paravertebral block. Br J Anaesth 1998;81:230–8.
*[18] Schnabel A, Reichl SU, Kranke P, et al. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2010;105:842–52.
*[19] Kairaluoma PM, Bachmann MS, Rosenberg PH, et al. Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesth Analg 2006;103:703–8.
[20] Costache I, Pawa A, Abdallah FW. Paravertebral by proxy - time to redefine the paravertebral block. Anaesthesia 2018;73:1185–8.
[21] Eason MJ, Wyatt R. Paravertebral thoracic block-a reappraisal. Anaesthesia 1979;34:638–42.
[22] Marhofer P, Kettner SC, Hajbok L, et al. Lateral ultrasound-guided paravertebral blockade: an anatomical-based description of a new technique. Br J Anaesth 2010;105:526–32.
[23] Ben-Ari A, Moreno M, Chelly JE, et al. Ultrasound-guided paravertebral block using an intercostal approach. Anesth Analg 2009;109:1691–4.
[24] Shibata Y, Nishiwaki K. Ultrasound-guided intercostal approach to thoracic paravertebral block. Anesth Analg 2009;109:996–7.
[25] Abdallah FW, Brull R. Off side! A simple modification to the parasagittal in-plane approach for paravertebral block. Reg Anesth Pain Med 2014;39:240–2.
[26] Yoshida T, Fujiwara T, Furutani K, et al. Effects of ropivacaine concentration on the spread of sensory block produced by continuous thoracic paravertebral block: a prospective, randomised, controlled, double-blind study. Anaesthesia 2014;69:231–9.
*[27] Uppal V, Sondekoppam RV, Sodhi P, et al. Single-injection versus multiple-injection technique of ultrasound-guided paravertebral blocks: a randomized controlled study comparing dermatomal spread. Reg Anesth Pain Med 2017;42:575–81.
[28] Naja Z, Lonnqvist PA. Somatic paravertebral nerve blockade. Incidence of failed block and complications. Anaesthesia 2001;56:1184–8.
[29] Pace MM, Sharma B, Anderson-Dam J, et al. Ultrasound-guided thoracic paravertebral blockade: a retrospective study of the incidence of complications. Anesth Analg 2016;122:1186–91.
[30] Offodile 2nd AC, Aycart MA, Segal JB. Comparative effectiveness of preoperative paravertebral block for post-mastectomy reconstruction: a systematic review of the literature. Ann Surg Oncol 2018;25:818–28.
[31] Versyck B, Groen G, van Geffen GJ, et al. The pecs anesthetic blockade: a correlation between magnetic resonance imaging, ultrasound imaging, reconstructed cross-sectional anatomy and cross-sectional histology. Clin Anat 2019;32(3):421–9.
*[32] Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. Anaesthesia 2011;66:847–8.

*[33] Kulhari S, Bharti N, Bala I, et al. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: a randomized controlled trial. Br J Anaesth 2016;117:382–6.
[34] Pawa A, Wight J, Onwochei DN, et al. Combined thoracic paravertebral and pectoral nerve blocks for breast surgery under sedation: a prospective observational case series. Anaesthesia 2018;73:438–43.
*[35] Blanco R, Parras T, McDonnell JG, et al. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. Anaesthesia 2013;68:1107–13.
[36] Bhoi D, Selvam V, Yadav P, et al. Comparison of two different techniques of serratus anterior plane block: a clinical experience. J Anaesthesiol Clin Pharmacol 2018;34:251–3.
[37] Biswas A, Castanov V, Li Z, et al. Serratus plane block: a cadaveric study to evaluate optimal injectate spread. Reg Anesth Pain Med 2018;43:854–8.
[38] Durant E, Dixon B, Luftig J, et al. Ultrasound-guided serratus plane block for ED rib fracture pain control. Am J Emerg Med 2017;35:197. e3-e6.
*[39] Madabushi R, Tewari S, Gautam SK, et al. Serratus anterior plane block: a new analgesic technique for post-thoracotomy pain. Pain Phys 2015;18:E421–4.
[40] Womack J, Varma MK. Serratus plane block for shoulder surgery. Anaesthesia 2014;69:395–6.
[41] Khemka R, Chakraborty A, Ahmed R, et al. Ultrasound-guided serratus anterior plane block in breast reconstruction surgery. A A Case Rep 2016;6:280–2.
[42] de la Torre PA, Garcia PD, Alvarez SL, et al. A novel ultrasound-guided block: a promising alternative for breast analgesia. Aesthet Surg J 2014;34:198–200.
[43] Ueshima H, Kitamura A. Blocking of multiple anterior branches of intercostal nerves (Th2-6) using a transversus thoracic muscle plane block. Reg Anesth Pain Med 2015;40:388.
[44] Dieguez Garcia P, Fajardo Perez M, Lopez Alvarez S, et al. Ultrasound-assisted approach to blocking the intercostal nerves in the mid-axillary line for non-reconstructive breast and axilla surgery. Rev Esp Anestesiol Reanim 2013;60:365–70.
[45] Elsharkawy H, Maniker R, Bolash R, et al. Rhomboid intercostal and subserratus plane block: a cadaveric and clinical evaluation. Reg Anesth Pain Med 2018;43:745–51.
[46] Costache I, Sinclair J, Farrash FA, et al. Does paravertebral block require access to the paravertebral space? Anaesthesia 2016;71:858–9.
[47] Forero M, Adhikary SD, Lopez H, et al. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med 2016;41:621–7.
[48] Tsui BCH, Fonseca A, Munshey F, et al. The erector spinae plane (ESP) block: a pooled review of 242 cases. J Clin Anesth 2018;53:29–34.
[49] Pfeiffer G, Oppitz N, Schone S, et al. Analgesia of the axilla using a paravertebral catheter in the lamina technique. Anaesthesist 2006;55:423–7.
[50] Juttner T, Werdehausen R, Hermanns H, et al. The paravertebral lamina technique: a new regional anesthesia approach for breast surgery. J Clin Anesth 2011;23:443–50.
[51] Zeballos JL, Voscopoulos C, Kapottos M, et al. Ultrasound-guided retrolaminar paravertebral block. Anaesthesia 2013;68:649–51.
[52] Voscopoulos C, Palaniappan D, Zeballos J, et al. The ultrasound-guided retrolaminar block. Can J Anaesth 2013;60:888–95.
[53] Murouchi T, Yamakage M. Retrolaminar block: analgesic efficacy and safety evaluation. J Anesth 2016;30:1003–7.
[54] Costache I, de Neumann L, Ramnanan CJ, et al. The mid-point transverse process to pleura (MTP) block: a new end-point for thoracic paravertebral block. Anaesthesia 2017;72:1230–6.
[55] van Diest PJ, van der Wall E, Baak JP. Prognostic value of proliferation in invasive breast cancer: a review. J Clin Pathol 2004;57:675–81.
[56] Nishizaki T, Matsumata T, Kanematsu T, et al. Surgical manipulation of VX2 carcinoma in the rabbit liver evokes enhancement of metastasis. J Surg Res 1990;49:92–7.
[57] Angele MK, Faist E. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. Crit Care (London, England) 2002;6:298–305.
[58] Melamed R, Rosenne E, Shakhar K, et al. Marginating pulmonary-NK activity and resistance to experimental tumor metastasis: suppression by surgery and the prophylactic use of a beta-adrenergic antagonist and a prostaglandin synthesis inhibitor. Brain Behav Immun 2005;19:114–26.
[59] Wu J, Lanier LL. Natural killer cells and cancer. Adv Cancer Res 2003;90:127–56.
[60] Meng S, Tripathy D, Frenkel EP, et al. Circulating tumor cells in patients with breast cancer dormancy. Clin Cancer Res 2004;10:8152–62.
[61] Deegan CA, Murray D, Doran P, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg Anesth Pain Med 2010;35:490–5.
[62] Buckley A, McQuaid S, Johnson P, et al. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study. Br J Anaesth 2014;113(Suppl 1):i56–62.
[63] Ecimovic P, Murray D, Doran P, et al. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. Br J Anaesth 2011;107:916–23.
[64] Juneja R. Opioids and cancer recurrence. Curr Opin Support Palliat Care 2014;8:91–101.
[65] Connolly C, Buggy DJ. Opioids and tumour metastasis: does the choice of the anesthetic-analgesic technique influence outcome after cancer surgery? Curr Opin Anaesthesiol 2016;29:468–74.
[66] Exadaktylos AK, Buggy DJ, Moriarty DC, et al. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006;105:660–4.
*[67] Chen WK, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PLoS One 2013;8:e56540.
*[68] Sun Y, Li T, Gan TJ. The effects of perioperative regional anesthesia and analgesia on cancer recurrence and survival after oncology surgery: a systematic review and meta-analysis. Reg Anesth Pain Med 2015;40:589–98.

[69] Perez-Gonzalez O, Cuellar-Guzman LF, Soliz J, et al. Impact of regional anesthesia on recurrence, metastasis, and immune response in breast cancer surgery: a systematic review of the literature. Reg Anesth Pain Med 2017;42:751–6.
[70] Tsigonis AM, Al-Hamadani M, Linebarger JH, et al. Are cure rates for breast cancer improved by local and regional anesthesia? Reg Anesth Pain Med 2016;41:339–47.
[71] Kairaluoma P, Mattson J, Heikkila P, et al. Perioperative paravertebral regional anaesthesia and breast cancer recurrence. Anticancer Res 2016;36:415–8.
[72] Cata JP, Chavez-MacGregor M, Valero V, et al. The impact of paravertebral block Analgesia on breast cancer survival after surgery. Reg Anesth Pain Med 2016;41:696–703.
[73] Koonce SL, McLaughlin SA, Eck DL, et al. Breast cancer recurrence in patients receiving epidural and paravertebral anesthesia: a retrospective, case-control study. Middle East J Anaesthesiol 2014;22:567–71.
[74] Starnes-Ott K, Goravanchi F, Meininger JC. Anesthetic choices and breast cancer recurrence: a retrospective pilot study of patient, disease, and treatment factors. Crit Care Nurs Q 2015;38:200–10.
[75] Finn DM, Ilfeld BM, Unkart JT, et al. Post-mastectomy cancer recurrence with and without a continuous paravertebral block in the immediate postoperative period: a prospective multi-year follow-up pilot study of a randomized, triple-masked, placebo-controlled investigation. J Anesth 2017;31:374–9.
[76] Weitzen S, Lapane KL, Toledano AY, et al. Principles for modeling propensity scores in medical research: a systematic literature review. Pharmacoepidemiol Drug Saf 2004;13:841–53.
[77] Sessler DI, Ben-Eliyahu S, Mascha EJ, et al. Can regional analgesia reduce the risk of recurrence after breast cancer? Methodology of a multicenter randomized trial. Contemp Clin Trials 2008;29:517–26.