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Cingulotomy for Cancer Pain

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Abstract

Background: Stereotactic anterior cingulotomy is a neurosurgical technique that can offer significant pain relief in patients with refractory cancer pain, particularly in the palliative setting. Despite being described in the 1960s, its use has recently resurged due to limitations of pharmacologic and neuromodulatory therapies in terminally ill patients. The anterior cingulate cortex plays a crucial role in the affective processing of pain, and its disruption through targeted lesioning may reduce suffering without eliminating nociception. **Summary:** This review summarises the historical background, patient selection criteria, surgical approaches, efficacy data, and safety outcomes associated with bilateral anterior cingulotomy for cancer-related pain. Additionally, the Queen Square approach, incorporating MRI-guided targeting and diffusion imaging, is described. Available data support the procedure's short-term efficacy in the majority of patients, with limited cognitive side effects and minimal morbidity. Future directions include network-based targeting, refinement of lesion techniques, and consideration of non-invasive alternatives such as focused ultrasound. **Key Messages:** Cingulotomy is a safe and effective procedure for cancer pain. Further research is warranted to optimise selection criteria and understand the neural mechanisms underlying pain relief.

Introduction

"I am not afraid of death, but I am afraid of dying". This is a sentiment often expressed by terminally ill cancer patients facing the inevitable. Whilst most of us accept that our time in this life must come to an end one day, we are justifiably fearful of dying in pain. A recent report by the United Kingdom Office of Health Economics concluded that "even if every dying person who needed it had access to the level of care currently provided in hospices, 6,394 people a year [in the UK] would still have no relief of their pain in the final three months of their life. This equates to 17 people in the UK dying in unimaginable pain every day."[1]

Stereotactic anterior cingulotomy is a safe and efficacious procedure that has been shown to alleviate diffuse cancer pain and reduce the need for high doses of opioids and sedatives towards the end of life. It was advocated for the treatment of intractable cancer pain in the 1960s. It acts by modulating pain perception and experience rather than sensation given that the anterior cingulate cortex (ACC) has a known role in pain affect[2], [3], [4], [5]. Moreover, the ACC is highly connected with pain and emotion-processing brain regions via the cingulum bundle, such as the amygdala, posterior insula, nucleus accumbens, periaqueductal grey, and the ventral tegmental area[6], [7]. Whilst a range of less invasive and neurostimulation-based neurosurgical strategies exist for managing cancer-related pain, there remains a subset of patients for whom all available options are either ineffective or not feasible[8]. In this review, we examine the use of bilateral anterior cingulotomy for cancer pain, evaluate the evidence for its efficacy and safety, and provide an outline of our present surgical approach.

Early history and rationale

The use of bilateral anterior cingulotomy for intractable pain evolved from observations that frontal lobotomy relieved chronic pain from as early as the first case series reported by Freeman and Watts[9]. In the progression towards a more limited procedure for neuropsychiatric disorders, resection of the cingulate gyrus (specifically, cingulate area 24) and undercutting of the cingulum bundle to isolate the cingulate gyrus were developed by Cairns and LeBeau, and Livingston, respectively[10], [11], [12], [13]. Foltz and White applied stereotactic bilateral and unilateral "cingulumotomy", which was achieved through closed electrocoagulation of the anterior portion of the cingulum bundle, to relieve neoplastic and non-neoplastic intractable pain in a cohort of 16 patients. The rationale was that the procedure would ease the "mental suffering" caused by physical pain in a similar manner to the efficacy of frontal lobotomy for neuropsychiatric disorders and addiction, greatly influenced by Papez's theory of circuits underlying emotion in the human brain[14]. Patients with cancer pain, in particular, were thought to have "strong emotional factors" contributing to their pain[15], [16]. On the observation that patients with the best outcomes in this cohort suffered from comorbid anxiety and/or depression, Ballantine *et al.* applied and developed radiofrequency (RF) ablation to perform bilateral anterior cingulotomy for a cohort of 57 patients with neuropsychiatric disorders to evaluate its efficacy, as well as its safety profile across a larger cohort including 12 patients with intractable pain[17]. The majority of case series published during this period and the following four decades contained a majority of patients with non-cancer pain[8], [16], [18], [19], [20], [21], [22]. The shift in performing cingulotomy primarily in the palliative setting in the early 2000s coincided with the rapid rise in opioid prescribing for non-neoplastic pain conditions, the advent of deep brain stimulation (DBS), and the backlash against lesioning procedures which accompanied these and similar pharmacologic and neuromodulation

advances[23], [24]. Whilst prior reported procedures relied on air ventriculography for stereotactic guidance during lesion placement, and later computer tomography (CT), the development of magnetic resonance image (MRI)-guided stereotactic bilateral anterior cingulotomy by Hassenbusch et al. in 1990 improved safety and efficacy in patients with cancer pain[25], [26]; **Fig 1**).

Stereotactic target development

It is important to highlight that there is no universal agreement on lesion placement, lesion volume, and overall number of lesions. Typically, lesions are placed bilaterally, ranging 17.5 - 37.5mm posterior from the tips of the frontal horns of the lateral ventricles and 5-13mm lateral from the midline[8]. The original approach by Ballantine et al. describes making a radiofrequency lesion 5cm superior to the roof of the lateral ventricle and a second one 1 cm deeper to the first[17]. To avoid the burden of reoperation for patients, Ballantine et al. and later Spangler et al. and Cosgrove et al. developed the double and triple lesion approach, or so-called 'six-pack' procedure, which involves making three lesions along the anteroposterior axis of the cingulum bundle bilaterally, for cingulotomy for the treatment of obsessive-compulsive disorder[27], [28], [29]. By the same reasoning for patients with cancer pain, Strauss et al., altered their approach from placing a single lesion 24mm behind the tips of the frontal horns to combining this with an additional more anterior lesion at 16mm, both 7-8mm from the midline[30]. Whilst a "sweet spot" for cingulotomy targeting has not been identified, a pooled linear regression analysis of reported cingulotomy lesion coordinates across studies has shown that pain outcomes worsened as a function of increased distance from the tips of the frontal horns[8].

Patient characteristics and selection

Decisions about whether a patient should undergo cingulotomy should involve a multidisciplinary team including but not limited to the treating oncologist, neurosurgeon, pain specialist, and palliative care physician[30]. Patients should have a reasonable life expectancy to benefit from the procedure and justify the surgical risk. This maybe four weeks or more but ideally patients should have a longer life expectancy when referred for the procedure. Patients with cancer pathology known to result in a significant burden of pain should be referred at an early stage of the disease (for example patients with pancreatic cancer, or metastatic sarcoma). Postoperative survival ranged from 3 days to 6 years across studies, however a large fraction of patients (60.3%) died in 3 months or less following cingulotomy across studies where this data was reported[8], [19], [30], [31].

Type of pain is not strictly defined although diffuse, nociceptive pain tends to respond better than neuropathic pain localised pain (though the latter can also be treated). Accordingly, the majority of cancer pain patients included across studies had diffuse pain syndromes due to widespread metastases. Where reported, these sites typically included the bones, lungs, and abdomen, with patient pain distributions covering large parts of the thorax, abdomen, back, and skeleton[26], [30], [31]. Pain should be refractory to best possible medical management within reason. For example, patients on high doses of opioids and sedatives may have pain relatively under control but this comes at the expense of drowsiness and other unacceptable side effects that impact quality of life, mobility, and engagement with relatives and loved ones towards the end of life. Moreover, restricted mobility could render patients unsuitable for oncological treatments such as radiotherapy. Other surgical options such as implantable morphine intrathecal pumps may also be unacceptable due to increased infection risk, wound healing complications, and MRI surveillance safety concerns post-operatively.

Evidence for efficacy and safety profile for cancer pain

Efficacy

Across 10 observational studies that reported postoperative pain outcomes, 72 out of 111 (65%) patients with cancer pain had "good" pain relief following anterior bilateral cingulotomy, in line with previous work and similar in efficacy for pain of non-neoplastic origin[8] (Table 1). Studies conducted prior to pain score standardisation clinically-assessed pain outcomes as either "poor", "fair", "good", or "excellent" as reported by the treating physician[16], [18], [19], [20], [32]. Five studies evaluated pain outcomes using standardised pain scoring systems including the Verbal Digital Pain Scale, Visual Analogue Scale, (VAS), McGill Pain questionnaire (MPQ), and Brief

Pain Inventory (BPI)[26], [30], [31], [33], [34]. Across studies that reported individual patient data points (n=24 patients), the median decrease in pain intensity score used was 66.7% (IQR: 77.8–40.9%), although only Strauss et al. reported time-to-postoperative follow-up as 1 month and Patel et al. followed each of 3 study patients up to 1 month, 2 weeks, and 4 months postoperatively until they died[26], [30], [31]. The field has historically defined a clinically significant reduction in pain as ≥30% decrease in patient-reported pain scores[35], [36], [37]. Given this, the data across these studies define 80% of patients as responders to cingulotomy. Similarly, Yen et al. reported that 80% of patients with cancer pain (n=15) had a >25% decrease in VAS or MPQ pain score at 1 month, which decreased to 59.1% at 3-month follow-up and 50% at 6-month follow-up, out of patients who were alive at these study timepoints (n=12 and 10, respectively)[33], [34]. Across all studies, this is estimated to be 60% of patients at 6-month follow-up, and 67% at 12 months[8]. Postoperative Karnofsky Performance Status (KPS) scores increased by a median of 25% (IQR: 41.4-0) across studies which reported these data for individual patients and suggests improvement in quality-of-life measures[26], [30].

Additionally, 5 studies reported opioid dose-related postoperative outcomes[16], [19], [30], [31], [38]. Out of 14 patients who were dependent on morphine due to pain in the first case series by Foltz and White, 9 did not experience morphine withdrawal symptoms following postoperative cessation of narcotics[16]. Hurt & Ballantine observed that cancer pain patients who achieved some pain relief through cingulotomy frequently ceased taking narcotics altogether[19]. Strauss et al. describe how patients administered intravenous morphine preoperatively were able to be weaned off to lower oral doses, aiding in their discharge from hospital, typically within 1-2 days for patients admitted electively from home[30]. However, an analysis including an additional cohort of patients operated at their centre demonstrated that there was no significant decrease in morphine equivalent daily dose (MEDD) between baseline and 1-month postoperative follow-up[38]. Patel et al. reported all relevant analgesic medication dosages at pre- and postoperative timepoints for the 3 patients that were operated, demonstrating that they achieved MEDD reductions of 58%-100%, though it is unclear which timepoints these data reflect and whether these improvements were sustained at final follow-up[31].

Complications

No studies reported any mortality attributable to or associated with cingulotomy, corroborated by the reported mortality and complications across 800 cingulotomies for primarily neuropsychiatric disease performed 1962-2003[29]. Common transient effects following cingulotomy included confusion, apathy, minor personality changes, and urinary incontinence. Four studies evaluated the impact of cingulotomy on neuropsychological function[18], [21], [30], [33] (Table 1). Cohen et al. reported significant impairments in attention, intention, spontaneous response production and naming tests at 3 and 12 months postoperatively in patients with non-cancer pain, however, cingulotomies were not performed under MRI-guidance and showed evidence of involving supplementary motor area (SMA) in some cases[21]. Both Yen et al. and Strauss et al. reported non-significant slight worsening of naming test performance at 1 month postoperatively and no significant changes in any other domain across a total of 16 cancer pain patients[30], [33]. In our experience, cancer patients tend to show paradoxical improvement in cognitive and executive functions following pain reduction and weaning off opioids and sedatives.

Reoperations

The proportion of patients who underwent reoperation following inadequate relief from initial cingulotomy was 7.6% of all initial cingulotomies reported for both cancer and non-cancer pain[8]. Though unreported, this proportion is likely much smaller for cingulotomy for cancer pain, given both the medical frailty and significantly shorter average life expectancy of this patient group as compared to patients with non-neoplastic pain. Across the two studies which report this data, two cancer pain patients underwent repeat cingulotomy at 6 and 4 weeks after initial operation[30], [31]. Strauss et al. performed repeat cingulotomy in 1/13 patients in their cohort, after which they altered their lesion placement to avoid reoperations in all remaining cancer pain patients[30].

Modern procedure at Queen Square

Operating on patients with advanced cancer poses significant challenges. These are patients often deemed unsuitable for neurosurgical interventions due to their significant comorbidities and short life expectancy. Local adjustments need to be taken into consideration to ensure patient safety and comfort. For example, in a specialised neurosurgical centre such as Queen Square, administering high doses of opioids on the surgical ward via infusion pumps is not a standard procedure. Moreover, some medications may not be readily available. This is important since some patients will be transferred for surgery from other cancer centres or hospices and an abrupt interruption in their medications may result in significant worsening of pain. It is therefore important to liaise with the palliative care team and specialist nurses to ensure continuity of care. Patients are generally consented on two separate occasions. The first consultation is carried out at the patient's local hospice or hospital at a time of day when they are least drowsy. They are given a patient information booklet, and their carers and family are involved in the discussion. A second consultation is carried out a few days later if patients would like to proceed with surgery and written consent is taken then. Pre-operative assessment will also include routine blood tests and anaesthetic assessments. Opioid medications are simplified and if possible, changed to short acting agents. These are then split into regular and as required administrations in order to monitor patient-initiated dose reduction following surgery and to prevent intoxication. Detailed preoperative neuropsychological tests are carried out pre-operatively and again three months following surgery.

Preoperative imaging includes acquiring Human Connectome Project style diffusion MRI (dMRI) sequences (1.5mm isotropic, 394 directions, Bval=1500, 3000), T1 (1mm isotropic), and T2 SPACE (1mm isotropic) sequences. These scans are then used to generate FAT1 scans to directly target the cingulate bundle (**Fig 2**)[39]. This is not strictly crucial and other centres may rely on structural MRI alone with or without tractography.
Surgery can be carried out awake or asleep. There is no intraoperative testing required, and patients can be lightly sedated for comfort. The decision to operate on the patient awake or asleep depends on anaesthetic risks (patients with lung metastases for example may have a high risk of incurring pulmonary complications from invasive ventilation whilst patients with spinal metastases may find it very painful to lie supine on the operating table, requiring general anaesthesia).

There is absolutely no role for microelectrode recording in this procedure. Surgery is carried out using a stereotactic frame and a stereotactic CT or MRI fused to the preoperative scan. If only structural MRI is used for targeting this can be acquired with the frame on the day without the need for other scans. Targeting in Queen Square is carried out using MRI guidance. The laterality (X coordinate) and depth (Z coordinate) is therefore guided by the location of the cingulate bundle. The anteroposterior location (Y coordinate) is set at 18mm anterior to the anterior commissure (AC).

Two burr holes are placed usually in front of the coronal suture, behind the hairline to achieve a perpendicular trajectory in the sagittal plane and a 10-20 degree angle in the coronal plane (lateral to medial). A round tipped radiofrequency probe (2mm diameter, 4mm electrode length) is inserted deep in the cingulate bundle to abut the corpus callosum. Fibrin glue is instilled in the burr holes to prevent CSF leak and brain shift. Lesions are created using a lesion generator using monopolar parameters of 80c for 60 seconds (bipolar lesioning using a bipolar electrode can be carried out in patients with contraindications to monopolar lesioning). The probe is then withdrawn by 3mm steps to create stacked lesions to cover the cingulate gyrus and the paracingulate gyrus if present (15-25%). A second trajectory using the same entry point may be required to achieve complete ablation of the cingulate bundle (a medial and a lateral trajectory). The procedure is then repeated on the other side. Small titanium plates are used to cap the burr holes. MRI is then taken to confirm lesion location and rule out an intracerebral haemorrhage.

Immediately following surgery, patients' pain and analgesic requirements are often unchanged (unlike following a cordotomy). Attention is paid to use of patient-initiated (as required) medications and generally, regular morphine doses are halved every two to three days. Efficacy in responders tends to peak at 10-14 days.

Ongoing challenges and future directions

There is significant heterogeneity across all studies, in terms of surgical technique used, number and location of cingulotomy lesions, and the pain and neuropsychological outcomes reported. In particular, the lack of

consistency in pain scoring systems used makes it difficult to objectively compare results across studies. The need for reporting richer patient pain data should be balanced with the fact that patients with advanced cancer may be too unwell, in too much pain, or somnolent from administered opioids to tolerate a demanding pain questioning protocol. At Queen Square, we work with patients to answer the VAS, BPI, MPQ, and neuropsychological battery pre- and post-cingulotomy, with the VAS, BPI severity, and tolerable neuropsychological testing as a minimum requirement for patients in whom the full protocol is not feasible. Similarly, Strauss et al. carry out VAS, BPI, palliative care outcome scale (POS), and neuropsychological testing as part of their assessments[30]. A substantial proportion of patients are lost to follow-up by 3 to 6 months due to disease progression and death, limiting the available evidence on long-term efficacy. Nevertheless, in the context of advanced cancer and limited prognosis, this may be less clinically relevant, particularly given the consistent evidence supporting the short-term analgesic benefit of cingulotomy which typically lasts until death[8], [30].

Moreover, very little is known about the mechanism by which cingulotomy results in pain alleviation. Recent work has shown that cingulotomy lesions modulate resting-state salience network functional connectivity by comparing patient-specific pre and postoperative resting-state functional MRI (rs-fMRI)[38]. Further work should be carried out to assess the degree to which modulation of connectivity within this network correlates with pain outcome and to delineate other clinically important brain-wide functional and structural connections disrupted by cingulotomy. The identification of a network of connections associated with successful pain alleviation could optimise lesion placement to maximally disrupt it.

Finally, like other lesion-based procedures, cingulotomy has undergone several technical refinements over time, evolving from open sectioning/ electrocoagulation to radiofrequency (RF) ablation, and more recently to laser interstitial thermal therapy (LITT)[31]. Magnetic resonance-guided focused ultrasound (MRgFUS) has emerged as a promising, non-invasive technique for intracranial lesioning, particularly for the treatment of essential tremor via thalamotomy[24]. MRgFUS creates precise, intracranial lesions without the need for craniotomy or skin incision, thereby minimising the risk of surgical complications. Nevertheless, existing technology is unable to create lesions in the cingulate due to the relatively superficial location of the target. Riis *et al*. describe administering low intensity FUS via a custom device to create transient anterior cingulate cortex lesions in 20 patients with chronic non-cancer pain within a double-blind crossover randomised control trial. Active treatment resulted in significantly greater pain relief than sham, with 75% patients experiencing a clinically meaningful reduction in numeric rating scale scores over the subsequent seven days[41]. This exciting new application of FUS would make it more feasible to conduct randomised controlled trials to evaluate efficacy in a more rigorous manner.

Limitations

The observational nature of all studies of cingulotomy for cancer pain to date and inclusion of data from case series limit the level of evidence available regarding its efficacy. However, we do not think that it is feasible or ethical to randomise treatment and carry out invasive sham surgery in this patient group in particular[8], [40]. However, the latent effect on pain reduction (usually 10 days after surgery) and the magnitude of reduction in pain scores and daily equivalent morphine dose supports an actual rather than a placebo effect.

Conclusion

Stereotactic bilateral anterior cingulotomy is an effective pain management strategy for patients with refractory cancer pain, especially given the advent of MRI-guidance, recent advances in surgical technique, and current use of advanced imaging targeting strategies. Future studies evaluating cingulotomy efficacy should report pain outcomes with widely-used, standardised pain scoring systems (e.g. BPI), as well as MEDD, and further investigate potential neuropsychological effects of cingulotomy. Further work is required to delineate the biological mechanisms underlying pain relief from cingulotomy, with particular focus on patient-specific brain connectivity studies in the overall aim of optimising targeting strategy for improved patient outcome.

Conflict of interest statement
The authors have no conflicts of interest to disclose relevant to the submitted work.

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Figure legends

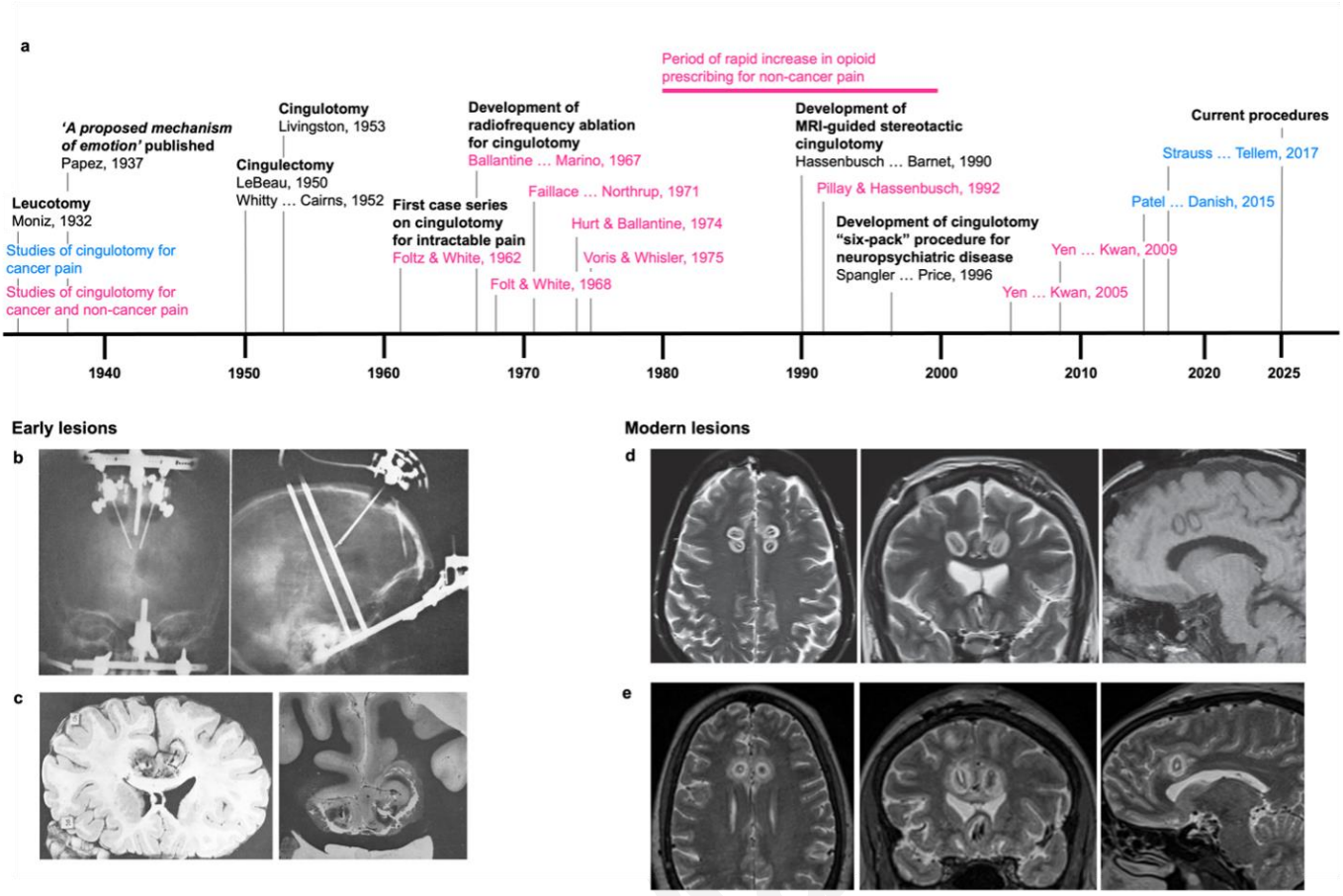
Fig. 1: A timeline of the evolution of cingulotomy for cancer pain and examples of early and modern cingulotomy lesions. **(a)** A timeline of events relevant to the evolution of stereotactic bilateral cingulotomy for cancer pain. Early lesions as made by Ballantine et al. by ventriculography-guided stereotaxy showing **(b)** coronal and sagittal view ventriculograms showing the placement of the RF probes to create a lesion, and **(c)** a post-mortem coronal cross-section of the brain of a patient who underwent cingulotomy alongside a Loyez stain slice of the same view to show the anatomical placement of the lesions[17]. Modern lesions made by MRI-guided stereotaxy shown in axial, coronal, and sagittal slices as performed by **(d)** Strauss et al.[30] and **(e)** at Queen Square.

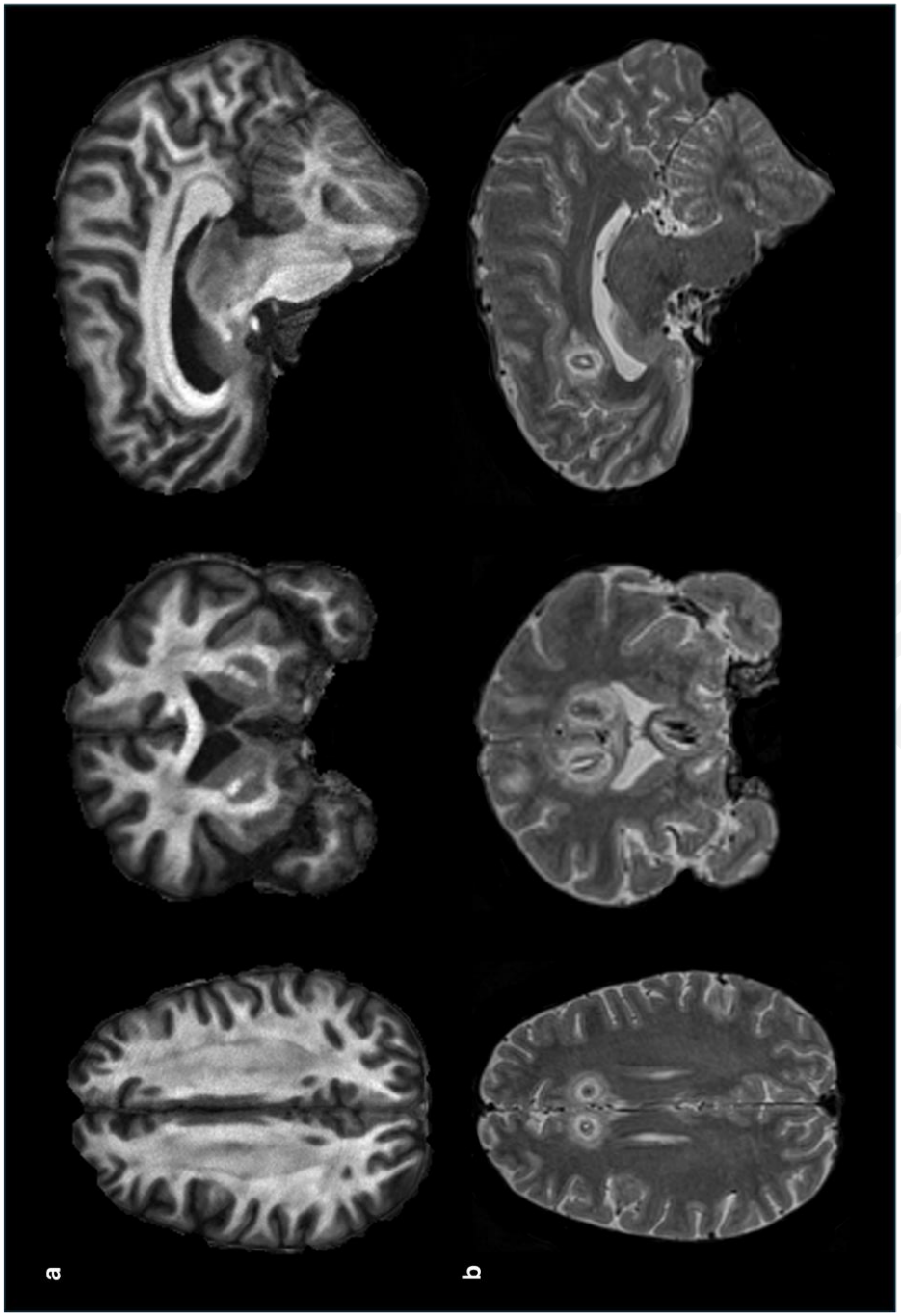
Fig. 2: Present cingulotomy lesion targeting approach at Queen Square. **(a)** Hybrid connectivity FA-T1 imaging is used to delineate the cingulum bundles bilaterally[39]. **(b)** Lesions placed to disrupt the entire depth and width of the cingulum bundle, including paracingulate branches, 18mm anterior to AC.

Authors & Year	No. of patients with cancer pain	Primary cancer diagnosis	Efficacy	Complications
Foltz and White, 1962[16]	6	Not stated	5 (83%) patients achieved ”good” pain relief	Not stated
Foltz and White, 1968[32]	11	Not stated	9 (82%) patients achieved ”good” pain relief	Not stated
Faillace et al., 1971[18]	7	Not stated	3 (43%) patients achieved ”good” pain relief	Not stated
Hurt and Ballantine, 1974[19]	32	Lung cancer: 7 Mouth carcinoma: 4 Laryngeal cancer: 3 Colorectal cancer: 3 Pancreatic cancer: 3 Uterine cancer: 2 Bladder cancer: 2 Pharyngeal cancer: 2 Melanoma: 2 Sarcoma: 2 Unknown: 1	18 (56%) patients achieved ”good” pain relief	Not stated
Voris and Whisler, 1975[20]	5	Not stated	5 (100%) patients achieved pain relief	Not stated
Pillay and Hassenbusch, 1992[26]	8	Breast cancer: 3 Skin cancer: Lung cancer: 1 Colorectal cancer: 1 Myeloma: 1 Chordoma: 1	5 (63%) patients achieved “good” pain relief	Not stated

Yen et al., 2005[34]	15	Breast cancer: 2 Hepatocellular carcinoma: 2 Mesothelioma: 2 Thyroid cancer: 1 Oesophageal cancer: 1 Ureteral cancer: 1 Lymphoma: 1 Unknown: 1	10 (67%) patients achieved >25% decrease in pain scores	Not stated
Yen et al., 2009[33]	10	Not stated	6 (60%) patients achieved >25% decrease in pain scores	Neuropsychological testing performed on all 10 patients revealed significant impairment of attention postoperatively at 1 week which improved and became nonsignificant by 1 month. 2 patients exhibited transient uninhibited speech lasting <2 days and 1 patient exhibited transient confusion postoperatively.
Patel et al., 2015[31]	3	Breast cancer: 1 Colorectal cancer: 1 Sarcoma: 1	2 (67%) patients achieved >30% in pain scores	Not stated
Strauss et al., 2017[30]	13	Sarcoma: 3 Parotid carcinoma: 2 Colorectal cancer: 2 Cervical cancer: 2 Chordoma: 1 Lymphoma: 1 Thyroid cancer: 1 Pancreatic cancer: 1 Non-small cell lung cancer: 1	9 (69%) patients achieved >30% in pain scores	Neuropsychological testing performed on 6/13 patients revealed a nonsignificant trend for decline in executive function and attention postoperatively. 4 patients exhibited transient confusion or mild apathy and 2/4 of these same patients also experienced urinary incontinence postoperatively.
Total	111	-	72	-

Table 1: Summary table of primary cancer diagnosis, efficacy, and complications of cingulotomy for cancer pain across studies.





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