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Review of intraoperative parathormone monitoring with the miami criterion: A 25-year experience

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Abstract

With the development of imaging and localization studies, focused parathyroidectomy with use of intraoperative parathormone monitoring (IPM) is the mainstay of treatment for primary hyperparathyroidism at many health care centers both nationally and internationally. Focused parathyroidectomy guided by IPM allows for surgical excision of the offending parathyroid gland through smaller incisions. The Miami criterion is a protocol that uses a "> 50% parathormone (PTH) drop" from either the greatest pre-incision or pre-excision measurement of PTH in a blood sample taken 10 min following resection of hyperfunctioning glands. Following removal of the hyperfunctioning parathyroid gland, a > 50% PTH drop at 10 min indicates completion of parathyroidectomy, and predicts operative success at 6 mo. IPM using the Miami criterion has demonstrated equal curative rates of > 97%, which is comparable to the traditional bilateral neck exploration. The focused approach, however, is associated with shorter recovery times, improved cosmesis, and lower risk of postoperative hypocalcemia.

Key words: Focused parathyroidectomy; Intraoperative parathormone monitoring; Primary hyperparathyroidism; Miami criterion; Localization studies

Core tip: Intraoperative parathormone monitoring (IPM) is vital component of the focused parathyroidectomy, the management of choice for primary hyperparathyroidism at the authors' institution. IPM is used to confirm complete removal of hyperfunctioning glands while preserving any remaining normally functioning glands before the operation is finished, guide the surgeon to continue neck exploration for additional hyperfunctioning glands when the intraoperative parathormone (PTH) levels do not drop sufficiently, identify parathyroid tissue by measurement of intraoperative PTH levels in fine needle aspiration samples, and lateralize hypersecreting parathyroid(s) through differential jugular venous sampling when preoperative localization studies are equivocal.

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BACKGROUND

In 1925, Dr. Felix Mandl performed the first excision of a parathyroid tumor in Vienna on patient Albert Jahne, a 34-year-old tramcar conductor suffering from osteitis fibrosa cystica who was admitted for a femur fracture[1]. Although he initially experienced a benefit from the parathyroidectomy, Jahne subsequently developed recurrent disease, possibly due to parathyroid carcinoma. He underwent reoperation in 1933, but ultimately died of uremia three years after this second surgical exploration[1]. Despite failing to achieve the desired clinical outcome, Jahne's case shifted the practice dogma towards surgery as the management of choice for primary hyperparathyroidism (pHPT). For most of the 19th century, the surgical treatment of pHPT was based on locating the four parathyroid glands intraoperatively and the excision of any grossly enlarged parathyroid glands while leaving all normal-sized glands *in situ*[2,3]. This qualitative approach that requires bilateral neck exploration (BNE) can be problematic, however, since parathyroid gland size and/or color does not always directly correlate to its secretory function[4,5]. If hypersecreting gland(s) are left behind, hypercalcemia will persist. Conversely, if all normal parathyroid glands are excised or their blood supply compromised during extensive BNE, postoperative hypocalcemia and tetany may occur. Today, when performed by experienced endocrine surgeons, BNE yields success rates of 95% to 99%[2,3].

With the advent of preoperative imaging modalities for the localization of hyperfunctioning glands, targeted or focused parathyroidectomy guided by intraoperative parathormone monitoring (IPM) is currently the standard treatment for patients with pHPT at numerous specialized centers both nationally and internationally[6-12]. This focused approach incorporates the common aspects of minimally invasive surgery resulting in limited surgical exploration, reduced operative time and less morbidity for patients with pHPT while maintaining comparable operative success rates to traditional BNE which ranges from 97% to 99%[6-10]. In general, focused parathyroidectomy is performed by creating a transverse cervical incision along the anterior neck which measures from 2 to 4 cm in those patients with one hyperfunctioning parathyroid gland identified by preoperative localization studies, sestamibi (MIBI) and/or ultrasound. When the offending parathyroid gland(s) is excised, an intraoperative parathormone (PTH) assay is used to confirm that there is no remaining hyperfunctioning tissue. When IPM levels drop by > 50%, usually at 10 min following abnormal parathyroid gland removal, the operation is concluded[13]. Focused parathyroidectomy guided by IPM can be achieved with either general or local anesthesia and can be performed in an ambulatory setting.

THE MIAMI CRITERION

In 1990, Irvin *et al*[14] refined and applied the intraoperative PTH immunoradiometric assay for the surgical management of pHPT after an unsuccessful parathyroid operation. His patient, who was the supervisor of the operating rooms, at the University of Miami/Jackson Memorial Hospital, had pHPT, and she approached Irvin to perform the operation. She underwent traditional BNE during which one large parathyroid gland was excised, and a second contralateral parathyroid gland was biopsied and preserved. Postoperatively, however, her serum calcium failed to normalize. Irvin spent the next 4 mo refining an intraoperative PTH assay to allow for results to be obtained within 15 min. He then took her back to the operating room and, by measuring intact PTH levels intraoperatively, was able to confirm removal of any remaining hyperfunctioning parathyroid glands and predict curative resection in this reoperative patient who had an intrathyroidal parathyroid gland in the contralateral lobe that was not appreciated in her initial operation[14].

In 1991, Irvin *et al*[15] would begin using IPM as a routine adjunct to focused parathyroidectomy at the University of Miami to reduce failure rates due to missed multiglandular disease (MGD). Having performed over 700 parathyroidectomies at that time, he attributed his failure rate of 7% to misdiagnosis or inability to excise all hyperfunctioning parathyroid gland tissue[15]. This intraoperative adjunct often termed the "quick PTH assay" takes advantage of the half-life of PTH which is approximately 3 to 5 min. Irvin further refined the PTH assay in 1993 to address the issue of long turnaround time for PTH results, which made previous attempts at intraoperative monitoring less practical[16,17]. Since then, the intraoperative "quick PTH assay" has undergone many modifications since the original immunoradiometric assay developed by Dr. Irvin. In current practice, intraoperative PTH is measured using a rapid immunochemiluminescence assay.

With the success and practicality of the intraoperative quick PTH assay, Irvin went on to describe the Miami criterion, a protocol that uses a "> 50% PTH drop" from either the highest pre-incision or pre-excision PTH measurement in a sample taken 10 min following complete resection of the hyperfunctioning glands. Following removal of the hyperfunctioning parathyroid gland, a > 50% PTH drop at 10 min indicates removal of the abnormal parathyroid glands, predicting operative success at 6 mo[13]. As a result, IPM allows for a focused or targeted approach to parathyroidectomy that involves surgical excision of the offending gland through smaller incisions with equal curative rates of > 97%

which is comparable to BNE[6-10]. The focused approach is also associated with fewer comorbidities including permanent hypoparathyroidism that may result from iatrogenic ischemia or injury to the remaining parathyroids during BNE.

At the University of Miami, the intraoperative PTH assay permits the surgeon to confirm excision of all abnormal parathyroid glands while preserving the remaining normally functioning parathyroid glands before the operation is finished; guide the surgeon to continue neck exploration for additional abnormal glands when the intraoperative PTH levels do not drop sufficiently; distinguish parathyroid from non-parathyroid tissue by measurement of intraoperative PTH levels in fine needle aspiration (FNA) samples; and lateralize hypersecreting parathyroid(s) to either side of the neck through differential jugular venous sampling when preoperative localization studies are equivocal.

IPM IN CURRENT PRACTICE

Surgeons must understand that the intraoperative PTH assay only measures the circulating amount of hormone from the location where blood samples are obtained and direct the sampling times related to the stages of the operative procedure. The "Miami criterion", which uses a "> 50% PTH drop" from either the greatest pre-incision or pre-excision PTH measurement in a sample of blood drawn 10 min following complete resection of a hyperfunctioning gland, requires peripheral venous or arterial access for blood collection at specific times during parathyroidectomy[13,16-18]. Intravenous access is maintained with a slow saline infusion that is discarded from the line to prevent dilution before any blood sample is quantified. Intraoperatively, at least 4 mL of peripheral whole blood sample in an EDTA specimen tube is collected at the following times: (1) a "pre-incision" level prior to skin incision; (2) a "pre-excision" level collected prior to clamping the blood supply to the abnormal gland; (3) a 5-min level; and (4) 10-min level after excision of the abnormal tissue. The samples should be promptly delivered to the laboratory for processing. With the efficiency and speed of the intraoperative PTH assay, point of care testing which measures PTH at the bedside is not performed at this institution.

When the PTH levels drop > 50% from the highest pre-incision or pre-excision value 10 min following the removal of the hyperfunctioning gland, this criterion predicts normal or low calcium measurements postoperatively with an overall accuracy of 98%[13]. After this "> 50% PTH drop" occurs, the surgeon terminates the operation without further identification of the normal parathyroid glands that remain. In the event that the PTH level at 10 min does not meet this criterion, an additional level may be obtained at 20 min and/or additional neck exploration can be performed until the removal of the remaining hyperfunctioning glands is determined by > 50% PTH drop from the highest subsequent pre-excision PTH measurement[19].

INTERPRETATION OF IPM DYNAMICS

A thorough knowledge of the disease process and careful interpretation of intraoperative PTH dynamics is required to effectively guide the surgeon during parathyroidectomy. The first example is of a 58-years-old woman with biochemical evidence confirming pHPT who presented with a PTH measurement of 107 pg/mL and a calcium level of 11.1 mg/dL on routine blood testing (Figure 1A). Her Tc-99m-sestamibi and ultrasound scans were concordant and suspicious for a right inferior parathyroid gland. An abnormal right inferior parathyroid was visualized intraoperatively, and this gland was carefully removed. Intraoperative PTH levels were drawn with the following measured values: Pre-incision 142 pg/mL; pre-excision 59 pg/mL; at 5 min 33 pg/mL, and at 10 min 25 pg/mL. The drop in Pre-excision level suggests the surgeon has identified the hyperfunctioning parathyroid gland as reflected in the > 50% PTH drop, which predicts operative success.

The next example is of a 45-year-old gentleman with biochemical confirmation of pHPT who presented with a calcium level of 10.8 mg/dL and PTH level of 125 pg/mL on routine blood tests (Figure 1B). His MIBI and ultrasound studies were concordant for a suspicious left inferior parathyroid. Intraoperatively, an abnormal left inferior parathyroid gland was located and excised with intraoperative PTH levels measured as follows: Pre-incision 109 pg/mL; pre-excision 170 pg/mL; at 5 min 51 pg/mL, and at 10 min 34 pg/mL. Unlike in the first case, the dramatic rise in pre-excision level, which was not observed in the previous example, suggests the surgeon has identified the hyperfunctioning parathyroid gland. During dissection, manipulation of the abnormal gland by the surgeon may have resulted in a sudden surge of PTH into the bloodstream reflected by a dramatic rise of pre-excision PTH level, it is important in this scenario to witness a drop in the PTH level on the subsequent 5 and 10 min samples. The patient's values ultimately reflect a > 50% PTH drop when compared to the pre-incision PTH level.

The final scenario is of a 34-years-old man who arrived to the emergency room with kidney stones (Figure 2). As a part of his evaluation, an elevated calcium level of 11 mg/dL and parathyroid hormone level of 119 pg/mL were measured. A preoperative MIBI scan did not localize an abnormal parathyroid gland. Following the excision of a right inferior parathyroid gland, intraoperative PTH levels drawn were: Pre-incision 173 pg/mL; pre-excision 150 pg/mL; at 5 min 143 pg/mL, and at 10 min 135 pg/mL. Without a > 50% PTH drop, exploration continued contralaterally and an abnormal left inferior parathyroid gland was discovered and excised. Intraoperative PTH levels were again measured and were as follow: Pre-excision 137 pg/mL; at 5 min 27 pg/mL; and at 10 min 19 pg/mL, confirming removal of hyperplastic parathyroid tissue

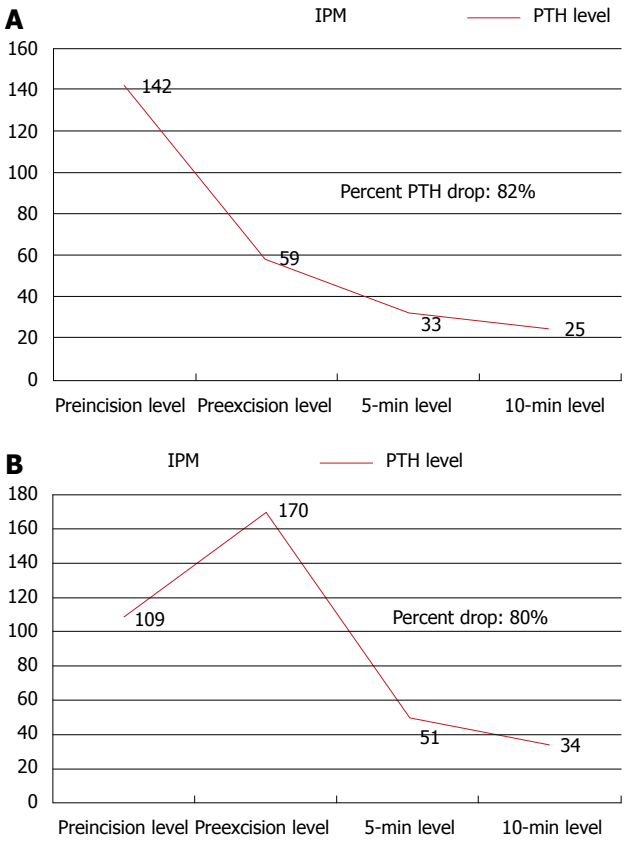

Figure 1 Intraoperative parathormone monitoring dynamics demonstrating a > 50% drop when compared to the pre-incision parathormone level using the Miami criterion. A: The drop of pre-excision PTH level suggests that the surgeon identified the hyperfunctioning gland during dissection reflected in the drop of PTH level; B: During dissection, manipulation of the abnormal gland may result in a release of PTH into the bloodstream, reflected by a surge in PTH level. It is important in this scenario to observe a drop in the PTH level on the subsequent 5 and 10 min samples from the higher pre-excision PTH level. IPM: Intraoperative parathormone monitoring; PTH: Parathormone.

with a > 50% PTH drop. As demonstrated in this case, when the PTH level fails to decrease > 50% from either highest pre-incision or pre-excision level, there should be a suspicion for MGD.

OTHER USES OF INTRAOPERATIVE PTH MEASUREMENT

Biochemical FNA

FNA of tissue for PTH measurement has valuable use in differentiating parathyroid glands from other tissues. During BNE or focused parathryoidectomy, biochemical FNA may be of value in identifying parathyroid tissue *vs* other tissues within the neck. When trying to differentiate between parathyroid from thyroid tissue or lymph nodes, this technique may be very helpful to the surgeon. A sample is obtained using a 25 gauge needle and diluted in 1 mL of normal saline. The sample is then sent to the laboratory where it is centrifuged. The PTH level is measured from the remaining supernatant after centrifugation[20]. As biochemical FNA has 100% specificity, this intraoperative technique can confirm parathyroid tissue more expeditiously than frozen section.

Internal jugular venous sampling

In the setting of discordant or negative preoperative localization imaging, differential venous sampling using the intraoperative PTH assay may allow surgeons to perform unilateral neck exploration in patients rather than BNE[21-23]. In order to lateralize the hyperfunctioning gland, bilateral internal jugular venous sampling of PTH is effective in directing surgical exploration. This procedure can be safely performed with ultrasound guided sampling of the inferior right and left internal jugular veins prior to skin incision. When there is a greater than 5% to 10% difference in PTH level, laterality to the side of the hyperfunctioning gland can be determined[21,22]. The surgeon may begin the operation by first exploring the identified side of the neck. The sensitivity of differential venous sampling approaches 80% according to published studies[21,22].

IPM and discordant localization studies

It has been argued that with the advancements in imaging modalities, combined preoperative localization with technetium Tc 99m sestamibi and ultrasound may eliminate need for IPM. In one retrospective cohort study of 569 patients with pHPT who underwent both MIBI and ultrasound, only 57% (n = 322) of patients had preoperative concordant localization studies and, in this group, there was a 99% success rate in achieving postoperative eucalcemia[24]. However, in 35% (n = 201) of patients with only one of two localization studies identifying an abnormal gland, neither MIBI nor ultrasound alone were able to correctly predict the location or extent of disease in 38% (76/201) patients in this discordant group. While there was marginal benefit among patients who had concordant preoperative localization imaging studies, IPM remained vital for patients with discordant studies undergoing limited parathyroidectomy[24]. In a retrospective series of 225 patients with pHPT where operative success was 97%, IPM remained an important adjunct for performing targeted parathyroidectomy in patients with discordant localization studies[25]. In a subgroup of 85 patients (38%) with discordant preoperative imaging, where IPM altered operative management and helped the surgeon during parathyroidectomy, operative success was 93%. In this series, IPM allowed surgeons to perform unilateral operation in 66% of patients, and confirmed excision of hyperfunctioning parathyroid glands in 7 patients with MGD[25].

LONG TERM OUTCOMES FOR IPM GUIDED PARATHYROIDECTOMY

Since 1993, parathyroidectomy has been guided by IPM for patients with pHPT at the University of Miami. BNE is no longer the initial approach in these patients with pHPT unless preoperative localization studies are negative or

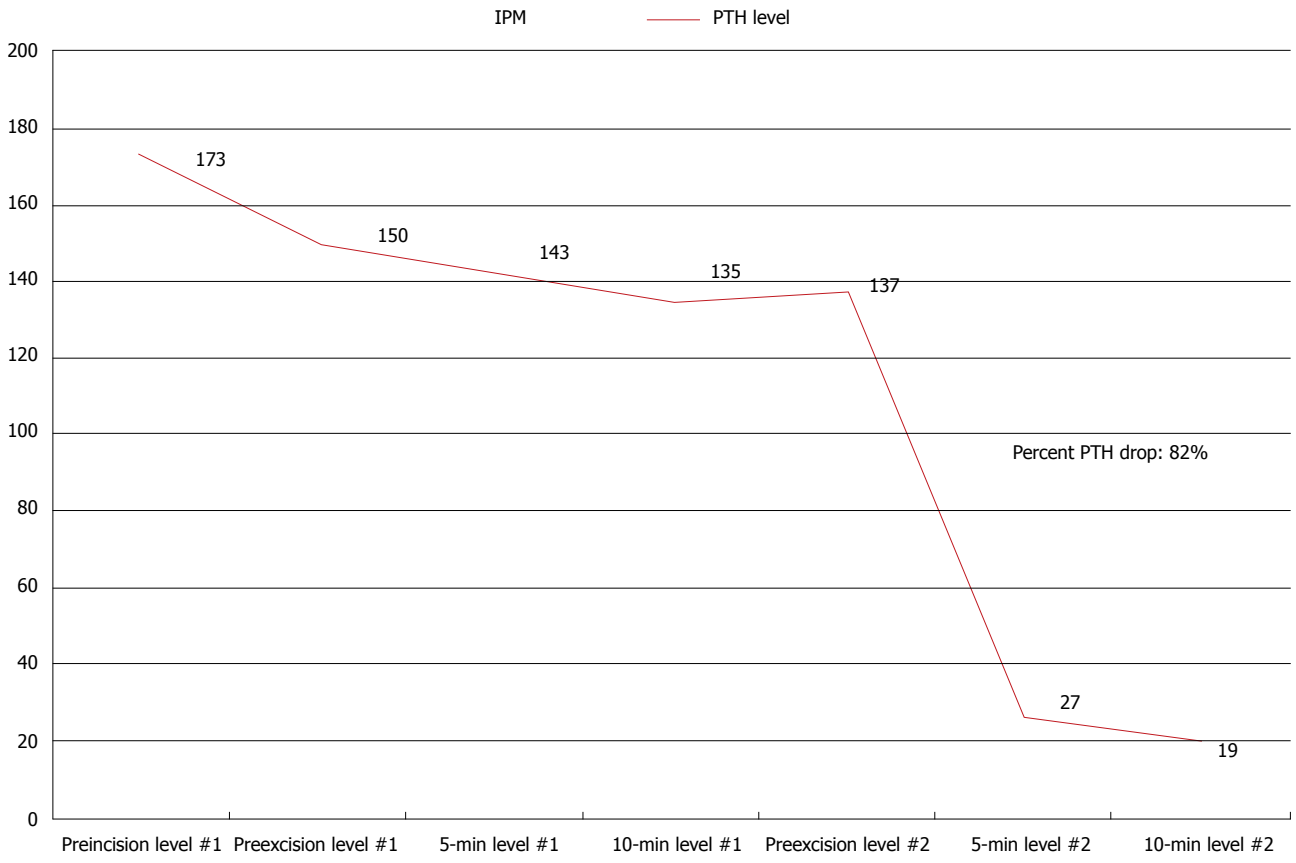

Figure 2 Intraoperative parathormone monitoring dynamics demonstrating > 50% drop using the Miami criterion when more than one abnormal parathyroid gland is removed. When the PTH level fails to drop > 50% from either pre-incision or pre-excision levels, there should be a suspicion for MGD. IPM: Intraoperative parathormone monitoring; MGD: Multiglandular disease; PTH: Parathormone.

when preoperative imaging has identified the wrong side of the neck. At the authors' institution, operative success is defined as calcium levels within normal limits for > 6 mo following successful parathyroidectomy. The definition of operative failure is persistent elevated PTH and elevated calcium measurements occurring < 6 mo following focused parathyroidectomy. Disease recurrence is defined as elevated PTH and elevated calcium measurements occurring > 6 mo following succes sful parathyroidectomy. The definition of MGD is two or more hypersecreting parathyroid glands identified intraoperatively during parathyroidectomy as demonstrated by IPM or if excision of one gland results in operative failure.

While criteria for IPM may vary among surgeons, the principle remains the same. By obtaining PTH levels in real time and achieving a desired reduction, the surgeon may have greater confidence intraoperatively that the offending hyperfunctioning parathyroid gland has been excised. While IPM has become common practice in most experienced centers, the Miami criterion has been compared to other stricter protocols in predicting post-operative eucalcemia. Stricter criteria proposed include a larger > 65%-70% PTH drop and/or return of absolute PTH level to within normal limits, or a PTH decrease at 5 min after gland removal[26-28]. In comparison to other criteria, the > 50% PTH drop was found to accurately predict operative success in > 95% of patients who had IPM guided parathyroidectomy for pHPT. In fact, the Miami criterion demonstrated the highest accuracy in predicting operative success when compared to other protocols, which included the Vienna, Rome, and Halle criteria[27]. In a study, which applied stricter protocols, the false positive rate would be reduced; however, at the expense of a lower sensitivity and an increased false negative rate. This false negative rate would then result in performance of BNE not necessary for the patient[29].

An additional protocol from the Mayo clinic was compared to different criteria in a study of 1882 patients with pHPT who had parathyroidectomy with IPM[30]. The Mayo criterion defined a successful parathyroidectomy as > 50% from baseline in addition to a normal or near-normal intraoperative PTH measurement at 10 min following removal of the abnormal gland. The Mayo criterion was compared with the following criteria for monitoring: A > 50% PTH drop at 10 min, > 50% PTH drop at 5 min, and intraoperative PTH within normal range at 10 min. The authors described an operative success of 97% equivalent to that of the Miami criterion. Results were similar when comparing Mayo criterion which had a sensitivity of 96%, PPV of 99%, and an accuracy of 95%, whereas the Miami criterion had had a sensitivity of 96%, PPV of 97%, and an accuracy of 94%. The criterion, however, differed with respect to

MGD. Authors reported that MGD was found in 271 patients (14.5%). A total of 134 of 1858 patients (7.2%) were not able to meet criteria predictive of cure, which indicated the presence of MGD. The authors reported that using the > 50% PTH criterion alone would have theoretically resulted in a failed parathyroidectomy in 22.4% of patients affected with MGD[30].

Critics of the focused parathyroidectomy predicted that the combination of both preoperative localization imaging studies and IPM would miss abnormal parathyroid glands, resulting in greater recurrence rates in patients undergoing parathyroidectomy. In a study of simulated focused parathyroidectomy, both preoperative sestamibi and ultrasound for localization and IPM were performed in all 916 patients with pHPT[31]. All patients underwent BNE, 16% of which had additional enlarged parathyroid glands. The researchers determined that the long term failure or recurrence rate of the focused approach may be greater than initially described in previous studies[31]. Other studies, however, demonstrated that focused parathyroidectomy had long-term surgical success that was similar to BNE. In another study of the 181 patients who underwent image-guided parathyroidectomy, no patients developed recurrent disease with a mean follow-up of approximately 5 years[32]. In a randomized clinical trial which had a five year follow-up, recurrence rates for targeted parathyroidectomy and traditional approach were 5% and 3%, respectively[30]. A study of 164 patients with an average follow-up of close to seven years demonstrated a 3% disease recurrence rate following successful focused parathyroidectomy guided by IPM[33]. Additionally, other studies found that parathyroid gland size or pathology do not show a correlation with PTH secretion reliably, as a result they may not be useful indicators for identifying hyperfunctioning parathyroid glands[4,5,34]. Together, such findings demonstrate that the focused parathyroidectomy has a durable operative success rate and does not miss MGD as a cause of disease recurrence. These postoperative outcomes indicate that IPM guided parathyroidectomy may allow for minimal dissection for patients with single gland disease in pHPT with durable long-term eucalcemia.

The implementation of IPM in patients with pHPT has shifted the surgical approach to parathyroidectomy from BNE to less invasive operations. Many studies have confirmed that the success of focused parathyroidectomy guided by IPM demonstrate operative success rates comparable to conventional BNE[6-10]. One study of 718 patients over thirty-four years demonstrated rates of operative success for focused parathyroidectomy and traditional approach to be 97% and 94%, respectively[6]. A review of 656 patients with 255 undergoing focused parathyroidectomy and 401 undergoing BNE demonstrated success rates of 99% and 97%, respectively[8]. The overall rates of complications for focused parathyroidectomy and BNE within this same study were 1.2% and 3%, respectively[8]. Patients who underwent focused parathyroidectomy experienced reduced operating room times of 1.3 h in contrast to patients undergoing BNE with operating times of 2.4 h[8]. There were shorter hospitalizations of 0.24 d for focused parathryoidectomy in comparison to 1.64 d for BNE[8]. Focused parathyroidectomy demonstrated equivalent long-term results when compared to conventional BNE for patients with pHPT in one randomized controlled trial with a 5-year follow-up[35].

CONCLUSION

Over the past 25 years, IPM has been an effective surgical adjunct that can be of help during parathyroidectomy in patients with pHPT. IPM has been shown to effectively confirm operative success with a focused or targeted approach that allows for minimal dissection and selected parathyroid gland excision. Using the Miami or "> 50% PTH drop" criterion, the surgeon excises only the hyperfunctioning parathyroid gland(s) without identifying the remaining normal parathyroid glands. Instead of identifying abnormal parathyroid glands by size, color, and/or pathology, IPM allows for quantitative recognition of parathyroid gland hyperfunction based on PTH secretion during parathyroidectomy where pHPT is recognized as a disease of function rather than form. IPM guided parathyroidectomy has become the preferred initial approach over traditional BNE, and there has been a shift of treatment paradigm from comprehensive to limited parathyroidectomy for pHPT over the last few decades. Parathyroidectomy guided by IPM has evolved into a highly successful and rapid operation, usually requiring minimal dissection that can be performed in an ambulatory setting. IPM has proven to be a vital adjunct to focused parathyroidectomy demonstrated by its high postoperative success rate and long term outcomes, and its efficacy ensures that this important tool will continue to benefit surgeons in the future.

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MINIREVIEWS

Patient handoffs in surgery: Successes, failures and room for improvement

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Abstract

Patient handoffs are transitions where communication failures may lead to errors in patient care. Face-to-face handoffs are preferred, however may not always be feasible. Different models and strategies have been described, yet there are few experimental studies. Expanding the problem, the on-call surgeon may be responsible for many patients, few or none that they admitted. Effective handoffs improve the quality of care and result in fewer errors. Herein we review different models of patient handoffs, comment on common pitfalls, and suggest areas for new research.

Key words: Patient handoff; Communication; Patient handover; Patient care; Face-to-face communication; Check out; Sign out

Core tip: Effective handoffs facilitate effective patient care. Distractions during handoffs cause errors in care, there are no outcomes data to recommend one type of handoff over another, and one type of handoff cannot satisfy all types of practice, even within the same institution.

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INTRODUCTION

Handoffs of patient care represent transition points where poor communication may lead to errors. The on-call surgeon may be responsible for many patients, few or none of whom they admitted. Communication barriers are the most frequent cause of handoff errors and may lead to adverse patient events[1]. Previous studies have demonstrated that there is omission of essential

patient information in up to 60% of handoffs[2,3]. Academic centers have faced challenges with handoffs since the implementation of the 80-h work week with more transitions in patient care[4]. With these work-restrictions and changes in health care economics and structure, there is a tendency towards more shift work, night team models, and cross coverage, thus reducing the continuity of care with the admitting physician or team. While reduced work hours may improve lifestyle, patient management can be compromised by communication errors and patient unfamiliarity. There is a paucity of studies that focus on physician-to-physician communication for transfer of patient care compared to the wealth of literature that addresses physician to patient communication[5,6]. Herein, we review the current status, pitfalls, and problems in patient handoffs.

Handoff definition

Although the meaning of a "handoff' is considered implicit by many, no common definition exists in the literature. Efforts have been taken to standardize the definition to facilitate data collection and research, but there is still no consensus[7]. Difficulties in standardizing a definition stem from what to include and exclude. Department- and hospital-specific needs differ considerably; for example, the essential information in a pediatric ward would be very different than that of a surgical intensive care unit. Cohen *et al*[7] provide one definition, "the exchange between health professionals of information about a patient accompanying either a transfer of control over, or of responsibility for, the patient". The Joint Commission defines the handoff process as a session "in which information about patient/client/resident care is communicated in a consistent manner"[8]. For the present work, we define a handoff as an on-call surgeon assuming the temporary care of another surgeon's patient - a vulnerable process that can be compromised by communication failures or individual errors.

Standardization of handoffs

Given that communication errors are well-known consequences of handoffs, the Joint Commission recommends standardization of handoffs; however, they do not provide examples or templates[7]. Similarly, many organizations recommend a standardized approach for patient handoffs, yet fail to provide any examples or what constitutes an effective handoff; one extensive review of the handoff literature failed to find a single instance of an organization providing a template for ideal handoffs[7]. Physicians seem to be amenable to standardized handoffs. In one survey study of emergency medicine program directors, the majority (72.3% of 185) agreed that a standardized handoff system may reduce errors, but most did not have standard policies in their own institution[9]. Data that show standardizations in handoffs improve patient outcomes are lacking. Any data that demonstrated the value of standardization would likely promote implementation. Changing well-established, individualized physician or service handoff practices to a standardized institutional handoff policy may impair, rather than improve efficiency since hospitals, units, and levels of care are vastly different. Given this, the majority of research on handoffs focuses on improvement within a single unit[1]. The on-call surgeon's burdens can be tremendous, especially with cross coverage with trauma and/or acute care surgery. Any process to standardize the handoff process would presumably improve patient care, although these processes should be individualized to particular institutions.

Surgical patient susceptible to errors in handoffs

The surgical patient is uniquely vulnerable to handoff errors because of the transient nature of their care, including the preoperative, perioperative, and postoperative transitions of care. There is a paucity of experimental surgery-specific studies on handoffs - Table 1 highlights some selected surgical studies. One study of 20 patients undergoing major gastrointestinal surgeries found a degradation in the transfer of patient information as the patients went from one phase of care to another[10]. There were failures of communication along all phases of care from preoperative period to postoperative handoffs, both of which had the highest number of communication failures. Fifteen of the 20 patients in that study had minor incidents or adverse events stemming from communication failures. Such errors may sometimes be due to differences in workflow as care is passed from the surgeon to the anesthesiologist and then back again to the surgeon on the wards or intensive care unit[2,10].

Concerning surgeon-to-surgeon handoffs, one study found that 28% of 146 patient adverse incidents in surgical care were attributed to handoffs[11]. Handoffs may not accurately identify problematic patients. One study that followed the sign-out sheets of one surgical residency program found that only 42% of adverse event occurred in patients identified as problematic - patients assigned to the on call team, believing they may be subject to complications[12]. As stated, surgical patients are inherently vulnerable to errors in handoffs with a high number of transitions in the preoperative, perioperative, to postoperative care periods. In addition, night float models often task the resident or attending surgeon to bear responsibility for many patients. In these settings, problems accumulate and are prioritized. The addition of a few urgent or emergent trips to the operating room leads to more opportunities for compromises in care. Prioritizing whether a patient with sudden shortness of breath *vs* another patient in the emergency room with pneumoperitoneum from a perforated ulcer deserves the on call surgeon's attention, all the while remember to check on yet another patient's serial cardiac enzymes is an example of the difficulty of the night float system.

Duty hours in residency programs

Since the implementation of the 80-h work week in

Table 1 Selected surgical handoff studies

Ref.	Design	Methods	Results
Johner *et al*[18]	Multi-center survey	Handoff practices of acute care surgery service in six Canadian general surgery residency programs	39 of 52 surveyed responded. 60% handoffs were mostly are always conducted face to face. Vast majority involved some kind of verbal communication
Zavalkoff *et al*[25]	Single-center implementation of handoff tool	Assess if implementing fill-in-the-blank handoff tool for pediatric heart surgery patients going to intensive care unit improved communication and adverse events	31 handoffs analyzed compared to handoffs prior to sheet. Following implementation of the tool, increase in detail of useful information transfer, no significant increase in time for handoff, lower rate of adverse events but did not reach significance
Scoglietti *et al*[12]	Single-center analysis of sign-out sheets	Resident sign-out sheets, which stratified problematic *vs* non-problematic patients, were collected over a 3-mo period. Patient outcome was analyzed	More non-problematic patients had adverse events, only 42% of adverse events occurred in the problematic patients
Al-Benna *et al*[19]	Multi-center telephone questionnaire	Handoff practices and quality by queried trainee surgeons at 30 British Isles burns units	Majority of units had junior-to-junior handoffs (76.7%), senior-to-senior trainee handoff (56.7%), and more than one level of trainee present. Few handoffs sessions were pager-free of interruptions (10%) and few had formal handoff training (16.7%)
Gawande *et al*[11]	Multi-center interviews	Interview of 38 surgeons from three academic teaching hospitals to identify errors that led to patient incidents	145 incidents reported, 43% (n = 62) of which were due to communication breakdown; of these 66% (n = 41) were due to handoffs errors

2003, general surgery residency programs have been challenged with developing schedules to minimize transitions in patient care. Night teams, float systems, and cross coverage have been implemented to adhere to the duty hour restrictions. This has caused a shiftwork mentality in some programs[4]. A study of malpractice claims showed that handoff errors are more common in teaching institutions[13]. Whether these errors are from ineffective handoffs or too many patients for the on-call resident to adequately care for, the end result is a resident unfamiliar with the patients and their specific needs[14]. Addressing these concerns, an Accreditation Council for Graduate Medical Education task force has made recommendations for residency programs to provide formal instructions for patient handoffs[4]. These include: Schedule designs to minimize the number of handoffs, offer clear documentation on how the handoff process is conducted, and make available the schedules of responsible residents and attendings[15]. Twenty-two of 29 surgical residents stated they perceived that patient care has been compromised by duty hour restrictions, however with improved perception of residents' quality of life[16]. Compromises in the continuity of care, a negative view of the night float system, and decreasing resident work ethics were major factors identified for decreased quality of patient care. The Johns Hopkins surgical residency program emphasizes a 10-point system for an effective handoff. Selected aspects of this 10-point system include: (1) allot adequate time for handoffs; (2) make the process active; (3) emphasize critically ill patients; (4) identify the chief resident on-call; and (5) only have a single standardized list[17]. Whether perception or reality that the limited work week compromises patient care, work hour restrictions is the system we are given - efforts must be made to optimize handoffs to improve the continuity of patient care.

Models of handoffs

There are several different models of handoffs, including, but not limited to, face-to-face and computer-assisted handoffs. Johner *et al*[18] reported a multi-institutional survey which queried handoff practices of acute care surgery service in six Canadian general surgery residency programs. They found that 60% of handoffs were mostly, or completely, conducted face to face. Further, the vast majority involved some form of verbal communication. However, these handoffs were rarely conducted in a quiet or private setting and over 25% of the time was interrupted. Another study surveyed surgeon trainees in 30 different burn units in the British Isles and found that the majority of units had junior to junior trainee handoffs (76.7%), senior to senior trainee handoff (56.7%), and more than one level of trainee present. Few handoffs sessions were free of pager interruptions (10%) and few participants had formal handoff training (16.7%)[19]. One study, evaluating internal medicine residents in four different hospitals, concluded that face-to-face handoffs are best for effectively communicating and reducing errors. Schouten *et al*[20] conducted a retrospective review that compared 305 patients who had a face-to-face handoff compared to 500 patients who were handed over using other methods. In their study, they found no difference in adverse events or mortality between the two groups. They hypothesize that providers that did not receive a dedicated face-to-face handoff may have spent more time familiarizing themselves with patients through other means. They also challenge the importance of face-to-face handoffs in a system where electronic medical records make all data available at one's disposal. Some authors advocate the use of computer-assisted handoffs. Flanagan *et al*[21] conducted a study with 35 internal medicine resident physicians in which computerized patient data were used to generate an electronic patient handoff tool. The objectives of this preliminary study included assessment of the completeness of the tool and the need for more information by the receiving physician. Findings

included that, often times, the report did not include the assessment and plan, and, in many cases, certain data were not accurately transferred. Distractions during handoffs increase the chance that working memory will fail, leading to a higher chance of subsequent medical errors[22]. Although face-to-face handoffs are felt to improve the receiving physician's perception of quality[23], data have not proven that face-to-face handoffs are associated with better patient outcome.

Current and future handoff research

Riesenberg *et al*[1] conducted a systematic review of physician handoffs in the United States. Their search yielded 46 articles, 33 of which were published since 2005. Only 18 of these 46 articles were experimental with the remainder being anecdotal experience, reviews, *etc.* Furthermore, their review revealed that only 6 of the 18 research articles had some measure of handoff effectiveness. Their study found that communication was the most frequently identified barrier to effective handoffs. Forty-five of forty-six articles involved residents or had a medical education theme. The status, problems, and differences in community hospitals are largely not reported in the literature[2]; this represents an area for future research.

One subject the literature on handoffs has yet to explore is the use of texting in communicating patient related care. The use of texting to communicate among residents and attendings was demonstrated in a single center survey study by Shah *et al*[24]. By surveying residents and attendings, they found that the majority of both residents (66%) and attendings (62%) used texting for patient-related care. Verbal or phone conversations were used more often for urgent or emergent situations, however, text messages were the primary means of communication of day-to-day practice of routine patient care. That study did not specifically address handoffs and there are no studies that we are aware of that have done so. Texting prevalence and other uses of smartphones in handoffs and comparison to other means would be a useful contribution to the literature.

CONCLUSION

From the literature, there is much stress on the importance of effective handoffs, yet few scientific studies. Several principles are clear: (1) distractions during handoffs cause errors in care; (2) there are no outcomes data to recommend one type of handoff over another; and (3) one type of handoff cannot satisfy all types of practice, even within the same institution. Areas for future work include data-driven experimental studies that compare different techniques of handoffs and their effects on patient care.

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Should multi-gene panel testing replace limited BRCA1/2 testing? A review of genetic testing for hereditary breast and ovarian cancers

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Abstract

Clinical testing of patients for hereditary breast and ovarian cancer syndromes began in the mid-1990s with the identification of the *BRCA1* and *BRCA2* genes. Since then, mutations in dozens of other genes have been correlated to increased breast, ovarian, and other cancer risk. The following decades of data collection and patient advocacy allowed for improvements in medical, legal, social, and ethical advances in genetic testing. Technological advances have made it possible to sequence multiple genes at once in a panel to give patients a more thorough evaluation of their personal cancer risk. Panel testing increases the detection of mutations that lead to increased risk of breast, ovarian, and other cancers and can better guide individualized screening measures compared to limited BRCA testing alone. At the same time, multi-gene panel testing is more time-and cost-efficient. While the clinical application of panel testing is in its infancy, many problems arise such as lack of guidelines for management of newly identified gene mutations, high rates of variants of uncertain significance, and limited ability to screen for some cancers. Through on-going concerted efforts of pooled data collection and analysis, it is likely that the benefits of multi-gene panel testing will outweigh the risks in the near future.

Key words: Panel testing; Genetic testing; *BRCA*; Breast cancer

Core tip: Evaluating multiple genes in a panel test has clear advantages over BRCA1/2 testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based

clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations, the ability to guide clinical decisions for patients will continue to improve.

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HISTORICAL CONTEXT

The first hereditary susceptibility gene associated with breast cancer risk was identified in 1994 and called *BRCA1*[1,2]. At that time, there were approximately 182000 cases of breast cancer diagnosed annually in the United States[3] and a growing concern to identify causative factors for a highly prevalent disease. Shortly thereafter in 1995, the *BRCA2* gene was identified and these two genes, *BRCA1* and *BRCA2* (*BRCA1/2*), began to play an important role in evaluating newly diagnosed breast cancer patients and others with high-risk family histories.

Initially, when clinical testing of *BRCA1/2* mutations began in 1996, there were many uncertainties and criticisms: Data to demonstrate outcomes and benefit of proposed management was still being gathered, directive guidelines did not exist, and understanding of the expanding phenotype and variable penetrance was still occurring. The rate of inconclusive results was higher, time to receive results was closer to two months, patient concern about genetic discrimination was much more pronounced, and protective legislation specific to genetic test results was limited. Furthermore, the long-term psychological impact of genetic testing results was yet unknown.

It is now well-documented that germline *BRCA1/2* mutations significantly increase risk for breast, ovarian, and male breast cancer as well as moderately increase risk for prostate and pancreatic cancer[4-6]. Established national guidelines identify which clinical histories warrant *BRCA1/2* genetic testing and how to manage patients who carry *BRCA1/2* mutations, specifically high-risk surveillance and risk-reducing surgical options[7]. *BRCA1/2* genetic testing is now routinely covered by insurance companies in patients with defined clinical histories, the rate of inconclusive results is less than 5%, and results are returned in approximately two weeks. Ultimately, a federal law was passed called Genetic Information Nondiscrimination Act "GINA" of 2008 to prevent medical insurance companies and employers from discriminating against individuals on the basis of their genetic information[8]. Fortunately, initial data has shown that no significant long-term psychological and emotional consequences occur as a result of genetic testing[9].

Many breast surgeons incorporate *BRCA1/2* testing into the initial work-up of newly diagnosed breast cancer patients who meet testing criteria to guide surgical decisions. Family members of affected individuals or other high-risk patients can also be easily referred for cancer genetic counseling for testing and preventive intervention strategies. The high prevalence of *BRCA1/2* mutations among male breast cancer patients and ovarian cancer patients has led to recommendations that any patient with one of these diseases obtain *BRCA1/2* testing[7]. In the last few years, testing criteria have also expanded to include pancreatic cancer and high-grade prostate cancer indications[7].

RECENT SHIFTS

Of hereditary breast cancers, only 30%-50% is attributed to mutations in *BRCA1* and *BRCA2* genes[10-12]. Over several decades of research, additional genetic mutations in numerous other genes have been implicated in breast and ovarian cancer risk. There are now over 20 genes and hundreds of mutations that have been implicated in the development of breast and/or ovarian cancer (Table 1)[12-14].

Traditionally, testing patients or those at risk for hereditary breast and ovarian cancer risk-began with evaluating *BRCA1/2*. If results were negative, additional testing was offered, often several weeks to months later, only if the patient met certain criteria for additional genetic syndromes. Numerous advances from scientific technology to legislation to public awareness and media, have shifted this testing paradigm.

Technological advances in DNA sequencing have come to what some have termed a "tipping point" in the advancement of genetic evaluation and discovery of new mutations related to hereditary cancer risk[15]. In place of more tedious methods of DNA sequencing using Sanger sequencing techniques, massively parallel DNA sequencing using Next Generation Sequencing (NGS) allows multiple genes to be evaluated at once.

With NGS, came the opportunity to offer panel testing, or evaluating numerous genes at once rather than in sequence. Panel testing decreased the turn-over-time for results while minimizing the cost of the test[10,13]. Even with panel testing, however, there were still restrictions with including *BRCA1/2* testing on a panel due to patents held by the founding company on evaluating these genes for almost 20 years. It was not until a 2013 Supreme Court ruling of Association for Molecular Pathology v. Myriad Genetics that many of these patents that restricted *BRCA1/2* testing became invalidated[16]. Since then, multi-gene panels offered by numerous genetic testing companies were able to include *BRCA1/2* in their panels and offer patients comprehensive testing upfront[17].

Another equally important event that occurred to influence hereditary genetic testing patterns was the public disclosure of the highly acclaimed actress Angelina

Table 1 List of select genes that can be found on multi-gene panels and associated cancer risks

Gene	Cancer risk[1]
ATM	Breast, pancreatic cancer
BARD1	Breast
BRCA1	Breast, ovarian, male breast cancer, melanoma, pancreatic cancer
BRCA2	Breast, ovarian, male breast cancer, melanoma, pancreatic, prostate cancer
BRIP1	Breast
CDH1	Breast, diffuse-type gastric cancer
CHEK2	Breast, colon, ovarian
EPCAM	Colorectal, uterine, stomach, ovarian
MLH1	Colorectal, uterine, stomach, ovarian
MRE11A	Breast
MSH2	Colorectal, uterine, ovarian
MSH6	Colorectal, uterine, stomach, ovarian
MUTYH	Breast, colorectal, other gastrointestinal sites
NBN	Breast
NF1	Breast, peripheral nerve sheath tumors, gliomas, leukemias, pheochromocytomas
PALB2	Breast, pancreatic cancer
PMS2	Colorectal, uterine, stomach, ovarian
PTEN	Breast, thyroid, endometrial cancer
RAD50	Breast
RAD51C	Breast, ovarian
RAD51D	Breast, ovarian
STK11	Breast, gastrointestinal, ovarian
TP53	Breast, ovarian, osteosarcomas, brain tumors, colorectal, other gastrointestinal sites

[1]List of cancer sites is not all-inclusive as additional sites may be pending further clinical validation.

Jolie's *BRCA1* mutation status in 2013. When Jolie explained her decision to choose prophylactic bilateral mastectomy and oophorectomy due to her *BRCA1* mutation, mainstream media brought public awareness to the importance of hereditary genetic testing and as a result, there became a surge in numbers of patients undergoing testing[18]. While numbers referred for testing have more than doubled in some locations, the majority of referrals have been found to be appropriate and for qualified candidates[18].

NEWER DATA

With this shift in testing, the clinical impact of multi-gene panel testing has become apparent. Prior to inclusion of *BRCA1/2* in panels, LaDuca *et al*[19] evaluated over 2000 patients who underwent multi-gene panel testing with 14-21 genes (excluding *BRCA1/2*) between March 2012 and May 2013. Overall, 8.3% of patients were found to carry pathogenic mutations, ranging from 7.2%-9.6% depending on the number of genes evaluated. Of patients who were deemed to be high risk for hereditary breast and ovarian cancer and underwent a "breast" panel with genes implicated in breast cancer pathogenesis, 10.9% of patients were found to carry pathogenic mutations. The genes found to be mutated most frequently in this cohort of high-risk patients included *PALB2*, *CHEK2*, and *ATM*.

Similarly, Tung *et al*[20] evaluated over 2000 high-risk patients who underwent a NGS multi-gene panel testing with 25 genes including *BRCA1/2*. Of patients who underwent panel testing with *BRCA1/2*, 9.3% were found to carry a *BRCA1/2* mutation and an additional 4.2% of patients carried non-*BRCA* mutations again with the most frequent gene mutations in *PALB2*, *CHEK2*, and *ATM*. Smaller studies have also shown the benefit of panel testing[14,21-23].

We have demonstrated that multi-gene panel testing nearly doubles the pathogenic mutation detection rate in patients with increased risk of hereditary breast and/or ovarian cancer when compared to limited *BRCA1/2* testing alone in a cohort of 966 high-risk patients[21]. Likewise, a French group used their own NGS panel of 27 genes to evaluate 708 high-risk patients and found a 15.4% mutation detection rate[14]. Mutations in *BRCA1/2* accounted for 59% of these genetic alterations in the French study, while 41% were non-*BRCA* genes, again most frequently in *PALB2*, *CHEK2*, and *ATM* genes.

When patients undergo panel testing with multiple genes, there is an increased detection of pathogenic mutations, but there is also increased detection of DNA variants of uncertain significance (VUS). Depending on the number of genes in a panel and the patients who are tested, VUS rates from panel testing have been reported to range from 6.7%-41.7%[19-21]. The VUS rate for any given gene will be highest initially as data starts to accumulate, then will decrease over time[19]. Nonetheless, *BRCA1/2* testing is still associated with a VUS rate of approximately 4%[21].

BENEFITS

In order for a new testing method to replace an es-

tablished algorithm, a substantial benefit should be possible with limited consequences. There are a number of obvious advantages of multi-gene panel testing over limited *BRCA1/2* testing. Panel testing not only provides patients with more information about their hereditary risk by increasing the detection of pathogenic mutations, but it also identifies actionable mutations for which patients can choose to increase surveillance of high risk cancers, initiate chemoprevention, or even undergo prophylactic surgery to remove a potential at-risk organ site.

Carrying a *BRCA1/2* mutation leads to a lifetime risk of breast cancer up to 85% and a lifetime risk of developing ovarian cancer between 15%-60%[4-6]. Increased surveillance with breast MRI can detect breast cancers at earliest stages for these patients, while prophylactic bilateral mastectomy decreases this risk by over 90% and prophylactic bilateral salpingo-oophorectomy minimizes the risk of both ovarian and breast cancer[24,25]. Similarly, patients with mutations in non-*BRCA* genes that are associated with increased risk of breast cancer, such as *PALB2*, *CHEK2*, and *ATM*, may also benefit from increased screening with breast MRI. Other patients with these non-*BRCA* gene mutations, especially those with a strong family history of breast cancer or who carry particularly penetrant gene mutations may even benefit from prophylactic mastectomies[26-31].

In addition to identifying genes associated with breast and/or ovarian cancer risk, panel testing identifies genes with cancer risk in other organ sites (Table 1). Mutations in the *PTEN* gene, for example, confer a risk of breast, thyroid, and endometrial cancer. Patients with *PTEN* mutations and the related Cowden syndrome are recommended to not only have increased breast cancer surveillance, but annual thyroid ultrasounds and endometrial evaluations as well[7]. On the other hand, *MSH2* mutations are implicated in Lynch syndrome, which is characterized by increased risk of early onset colon, uterine, and ovarian cancers[32]. For these patients, consideration of hysterectomy and oophorectomy and increased frequency of colonoscopies should be included in counseling. Multi-gene panel testing can help direct focused screening in high risk patients and even enable risk-reducing interventions.

Other benefits of panel testing over sequential testing include the ability to test for genes that a patient might not normally be considered for. This is especially true for more rare gene mutations that are typically associated with particular family inheritance patterns or traits such as Li Fraumeni syndrome or Cowden Syndrome[33,34]. With panel testing, these rare mutation carriers can be more readily identified in patients with limited or unknown family history.

Fortunately, NGS allows for multi-gene panel testing to be both efficient and cost-effective[13,23,35]. Rather than thousands of dollars for only *BRCA1/2* testing, dozens of genes can now be sequenced at once for a fraction of the cost.

LIMITATIONS AND CONCERNS

While panel testing increases the diagnostic yield by up to 50% compared to *BRCA1/2* testing alone, sometimes the pathogenic mutation identified is in a gene for which there is limited data as to the cancer risks and cancer spectrum so patient management recommendations will not be available. National Comprehensive Cancer Network guidelines currently provide detailed recommendations for a handful of well-characterized, highly-penetrant genes (*BRCA1, BRCA2, PTEN, TP53, CDH1,* and *STK11*) and also provide breast and ovarian management considerations for some of the genes commonly identified by panel testing (*ATM, CHEK2*, and *PALB2*)[7]. Detailed recommendations, however, accounting for the other cancer risks associated with these genes and recommendations for management of patients with mutations in less-characterized genes do not yet exist. It is also possible that mutations in moderate/intermediate-risk genes may not entirely explain a personal and/or family history of cancer; the role of gene/gene and gene/environment interactions could influence the manifestation of a gene mutation and/or cause phenocopies in the family (people who do not carry a known familial mutation but develop a cancer associated with the familial gene mutation). In addition, others have argued that there is a lack of clinical validity due to limited data sets that estimate cancer risk for many of the genes found on panels[36]. Clearly larger population and family-based studies will be needed to provide the best risk-estimates for appropriate counseling for the more rare gene mutations. Given this, management recommendations for patients (and their family members) with mutations in less-characterized genes need to take into account what is known about the specific gene as well as the personal and family clinical history[21].

With the identification of cancer risk outside of breast, colon, and ovarian cancer, comes the question of how to screen for and/or prevent rare cancers that associated with specific gene mutations (Table 1). This dilemma is not specific to the "newer" genes included on many panels. Patients with a *BRCA1/2* gene mutation and family history of pancreatic cancer are counseled that they likely have an increased risk for pancreatic cancer, but screening for early-detection of pancreatic cancer is not well-established and only recommended within the scope of a clinical trial[37]. Patients found to carry a *TP53* gene mutation are informed that they have a significantly elevated risk for multiple types of cancers, some of which we have screening modalities and guidelines for but others which do not[7]. On the other hand, patients with a *CDH1* gene mutation can have up to a 70% risk of gastric cancer by age 80 and may be recommended to consider prophylactic total gastrectomy[38]. As with targeted *BRCA1/2* or *TP53* testing, patients undergoing panel testing need to be informed of the benefits, limitations, and possible implications of testing, including limited screening and

prevention options for certain cancers.

Another limitation with panel testing is the higher rate of inconclusive (variant of uncertain significance) results. Similar to the early days of *BRCA1/2* genetic testing when VUS rates were higher, clinicians ordering panels for their patients must be aware of the higher possibility of identifying a VUS and make empiric management recommendations based on the personal and family clinical history when such a result is received[19-22]. An inconclusive result can cause patient (and clinician) anxiety about future cancer risks and potential risk for family members. Patients with VUS results can contribute to research specific to their gene variant and participate in national registries such as the Prospective Registry of Multiplex Testing. Often, however, facilitation of patient participation in such research falls to the managing busy clinician. As additional data is accumulated, VUS results are ultimately re-classified to either benign or deleterious, often years later, and the original ordering clinician receives the reclassification report that they must then act upon.

Lastly, as with any emerging technology, NGS and multi-gene panel tests are currently without established insurance guidelines for payment reimbursement. Without a panel-specific current procedural terminology (CPT) code, billing for panel tests is not as straightforward as *BRCA1/2* or Lynch testing for which gene-specific CPT codes exist. Obtaining authorization for *BRCA1/2* testing is fairly simple, while obtaining authorization for panel testing may require more work from the clinicians' office, although some laboratories will perform insurance authorization services to support the process.

CONCLUSION

Evaluating patients at risk for hereditary breast and ovarian cancer syndromes has transformed in a short period of time. Mutations in *BRCA1/2* genes are still the most common gene mutations accounting for inherited cancer risk, however numerous other genes have been added to the spectrum of hereditary cancer risk. Evaluating multiple genes in a panel test has clear advantages over *BRCA1/2* testing including a greater likelihood of identifying patients with actionable pathogenic mutations, improved efficiency over sequential testing, and lower overall cost. At the same time, panel testing comes with limitations; most notably a lack of clear management guidelines for mutations in moderate penetrance genes and limited evidence-based clinical validity. As more information is gathered on these moderate- and low-penetrance gene mutations and VUS through national efforts, our ability to guide clinical decisions for our patients will continue to improve. In the interim, thoughtful application of existing guidelines for gene mutations with cancer risk profiles similar to genes with established guidelines can be applied in the management of patients with mutations in some of these newer genes.

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ORIGINAL ARTICLE

Retrospective Study

Surgical outcomes of pulmonary resection for lung cancer after neo-adjuvant treatment

Benedetto Mungo, Cheryl K Zogg, Francisco Schlottmann, Arianna Barbetta, Craig M Hooker, Daniela Molena

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Abstract

AIM: To evaluate the outcomes of surgery for lung cancer after induction therapy.

METHODS: Using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database (2005-2012), we identified 4063 patients who underwent a pulmonary resection for lung cancer. Two hundred and thirty-six (5.8%) received neo-adjuvant therapy prior to surgery (64 chemo-radiation, 103 radiation alone, 69 chemotherapy alone). The outcomes were compared to 3827 patients (94.2%) treated with surgery alone. Primary outcome was 30-d mortality, and secondary outcomes included length of stay, operative time and NSQIP measured postoperative complications.

RESULTS: Lung cancer patients who received pre-

operative treatment were younger (66 *vs* 69, $P < 0.001$), were more likely to have experienced recent weight loss (6.8% *vs* 3.5%; $P = 0.011$), to be active smokers (48.3 *vs* 34.9, $P < 0.001$), and had lower preoperative hematological cell counts (abnormal white blood cell: 25.6 *vs* 13.4; $P < 0.001$; low hematocrit 53% *vs* 17.3%, $P < 0.001$). On unadjusted analysis, neo-adjuvant patients had significantly higher 30-d mortality, overall and serious morbidity (all $P < 0.001$). Adjusted analysis showed similar findings, while matched cohorts comparison confirmed higher morbidity, but not higher early mortality.

CONCLUSION: Our data suggest that patients who receive neo-adjuvant therapy for lung cancer have worse early surgical outcomes. Although NSQIP does not provide stage information, this analysis shows important findings that should be considered when selecting patients for induction treatment.

Key words: Lung cancer; Pulmonary resection; Neo-adjuvant therapy; Surgical outcomes

Core tip: The aim of this retrospective study was to evaluate the results of lung cancer patients undergoing surgery after induction treatment. Using the American College of Surgeons National Surgical Quality Improvement Program database, we identified 4063 patients who underwent lung resection for cancer. Two hundred and thirty-six (5.8%) underwent neo-adjuvant therapy. The results were compared to 3827 patients (94.2%) who underwent upfront surgery. On unadjusted and adjusted analysis, neo-adjuvant patients had significantly higher 30-d mortality, overall and serious morbidity than patient treated with surgery alone. Matched cohorts comparison confirmed higher morbidity, but not higher early mortality.

Mungo B, Zogg CK, Schlottmann F, Barbetta A, Hooker CM, Molena D. Surgical outcomes of pulmonary resection for lung cancer after neo-adjuvant treatment. *World J Surg Proced* 2016; 6(2): 19-29 Available from: URL: http://www.wjgnet.com/2219-2832/full/v6/i2/19.htm DOI: http://dx.doi.org/10.5412/wjsp.v6.i2.19

INTRODUCTION

Lung cancer is among the highest reason of cancer-related mortality in the United States, including about 27% of all cancer deaths in 2014, and 224210 estimated new cases in the same year[1].

Surgery represents the mainstay of treatment for lung cancer and ongoing advancements in surgical techniques across the last two decades have led to a remarkable reduction in operative mortality[2]. Lung cancer-related mortality, however, remains disappointingly high, showing a 5-year relative survival of about 15%[3].

In an attempt to improve survival for this disease, several multimodality treatment approaches, including neo-adjuvant therapy protocols, have been developed through the years. Given its potential benefits, such as clearance of micrometastasis and tumor downstaging, the efficacy of induction treatment has been evaluated with many trials; unfortunately the results have been controversial, hence the use of neo-adjuvant therapy for locally advanced disease still represents the subject of an ongoing debate[4]. Reluctance towards the use of induction is in part due to a perceived increase in surgical risk for lung cancer patients undergoing neo-adjuvant treatment. It has in fact been reported that, in this population, induction may lead to non-negligible treatment-related mortality, and increased occurrence of post-operative adverse events such as air leaks and infectious complications[5-7]. The concern of developing life-threatening complications, prevalent and severe enough to offset the potential benefits of induction, can constitute a significant obstacle for the diffusion of neo-adjuvant protocols. In this regard, an analysis of the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database has demonstrated that neo-adjuvant treatment is underutilized in the United States[8]. Only less than 10% of all major lung resections for primary lung cancer were reported to be preceded by induction treatment and, even for clinical stage ⅢA-N2, the percentage barely topped 50%. We queried the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, to evaluate the effects of neo-adjuvant treatment on 30-d outcomes of resection for lung cancer in the United States.

MATERIALS AND METHODS

The study consisted of a retrospective research database review using the 2005-2012 ACS-NSQIP. The ACS-NSQIP is a large, nationally-validated, risk-adjusted, outcomes-based program used to measure and improve the quality of surgical care. It collects data from approximately 500 collaborating hospitals each year that vary in size and academic affiliation[9]. At participating institutions, trained surgical/clinical reviewers abstract data *via* a process of prospective systematic collection that includes information on 135 patient demographic, preoperative risk factor, laboratory value, and intraoperative factor variables in addition to 30-d measures of postoperative morbidity and mortality. Surgical cases from multiple specialties are sampled using an ACS-validated, systemic sampling protocol. Standardization of methods, data field definitions, and data collection are ensured by training and auditing protocols as well as regular assessment of inter-rater reliability. Details of the ACS-NSQIP are described elsewhere[10]. The study was deemed exempt from ethical review by the Johns Hopkins University School of Medicine Institutional Review Board.

The study population was restricted to include patients

Table 1 Baseline demographic and clinical characteristics

Characteristic	Total n = 4063	Neoadjuvant patients n = 236 (5.81%)	Surgery-only patients n = 3827 (94.19%)	P-value[1]
Age (yr), median (IQR)	68 (61-75)	66 (55-72)	69 (61-75)	< 0.001[2]
Male (%)	2003 (49.30)	125 (52.97)	1878 (49.07)	0.246
Race (%)				
White	3019 (74.30)	189 (80.08)	2830 (73.95)	0.173
Black	222 (5.46)	12 (5.08)	210 (5.49)	
Latino(a)	432 (10.63)	17 (7.20)	415 (10.84)	
Other or unknown	390 (9.60)	18 (7.63)	372 (9.72)	
ASA classification (%)				
1-2 no-mild disturbance	769 (18.97)	38 (16.24)	731 (19.14)	0.523
3 serious disturbance	2888 (71.24)	171 (73.08)	2717 (71.13)	
4-5 life threatening/moribund	397 (9.79)	25 (10.68)	372 (9.74)	
Functional status				
Independent	3985 (98.08)	229 (97.03)	3756 (98.14)	0.227
Partially/totally dependent	78 (1.92)	7 (2.97)	71 (1.86)	
Obese, BMI ⩾ 30 (%)	1155 (28.65)	58 (24.79)	1097 (28.88)	0.178
Diabetes (%)	598 (14.72)	27 (11.44)	571 (14.92)	0.143
Current smoker (%)	1448 (35.64)	114 (48.31)	1334 (34.86)	< 0.001[2]
Alcohol consumption (%)	221 (5.44)	15 (6.36)	206 (5.38)	0.522
Dyspnea (%)	1106 (27.22)	57 (24.15)	1049 (27.41)	0.275
History of COPD (%)	1082 (26.63)	54 (22.88)	1028 (26.86)	0.179
History of heart disease (%)	42 (1.03)	3 (1.27)	39 (1.02)	0.734
Hypertension (%)	2375 (58.45)	111 (47.03)	2264 (59.16)	< 0.001[2]
Previous cardiac surgery (%)	308 (7.58)	11 (4.66)	297 (7.76)	0.081
Weight loss (%)	152 (3.74)	16 (6.78)	136 (3.55)	0.011[2]
Steroid use (%)	161 (3.96)	22 (9.32)	139 (3.63)	< 0.001[2]
Year of operation (%)				
2005-2008	834 (20.53)	53 (22.46)	781 (20.41)	0.662
2009-2010	1794 (44.15)	105 (44.49)	1689 (44.13)	
2011-2012	1435 (35.32)	78 (33.05)	1357 (35.46)	
Preoperative WBC (%)				
Normal (4.5-11.0 × 10^9/L)	3364 (85.88)	174 (74.36)	3190 (86.61)	< 0.001[2]
Abnormal (< 4.5 or > 11.0 × 10^9/L)	553 (14.12)	60 (25.64)	493 (13.39)	
Preoperative hematocrit (%)				< 0.001[2]
Normal (⩾ 36)	3147 (80.53)	110 (47.01)	3037 (82.66)	
Abnormal (< 36)	761 (19.47)	124 (52.99)	637 (17.34)	
Surgery type (%)				< 0.001[2]
VATS	1203 (29.61)	34 (14.41)	1169 (30.55)	
Open	2860 (70.39)	202 (85.59)	2658 (69.45)	

[1]P-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]Two-sided values < 0.05 considered statistically significant. Wilcoxon rank-sum test used to compare rank sum differences in the non-normal distribution of age. Different denominators due to missing data: ASA (n = 4054); obese (n = 4032); WBC (n = 3917), hematocrit (n = 3908). ASA: American Society of Anesthesiology; COPD: Chronic obstructive pulmonary disease; WBC: White blood cell (count); VATS: Video-assisted thoracic surgery; BMI: Body mass index; IQR: Interquartile range.

≥ 18 years of age with a primary diagnosis of lung cancer (according to International Classification of Diseases, 9th revision, Clinical Modification), who underwent pneumonectomy [defined by Current Procedural Terminology (CPT) codes: 32440, 32442, 32445, 32488, 32671], lobectomy (32480, 32482, 32486, 32503, 32504, 32663, 32670), segmentectomy (32484, 32669), or wedge resection (32505, 32506, 32666, 32667). Patients were further excluded if they lacked reported information on administration of chemotherapy (defined by the ACS-NSQIP to be chemotherapy within 30 d pre-operation) or radiotherapy (defined by the ACS-NSQIP to be radiotherapy within 90 d pre-operation).

Collected baseline demographic and clinical characteristics are reported in Table 1. They include: Age (years), gender, race (White, Black, Latino/a, other/unknown), American Society of Anesthesiology (ASA) classification (1/2 no-mild disturbance, 3 serious disturbance, 4/5 life-threatening/moribund), functional status (independent *vs* partially/totally dependent), obesity (defined as a BMI > 29 kg/m^2), diagnosis of diabetes, current smoker within 1 year, alcohol consumption (defined as > 2 drinks/d in the 2 wk prior to admission), dyspnea, history of chronic obstructive pulmonary disease, history of heart disease (congestive heart failure and/or myocardial infarction), hypertension requiring medication, previous cardiac surgery, > 10% loss of body weight in the last 6 mo, steroid use for a chronic condition, year of operation (2005-2008, 2009-2010, 2011-2012), preoperative white blood cell (WBC) count [normal (4.5-11.0 × 10^9/L) *vs* abnormal (< 4.5 or > 11.0 × 10^9/L)], [preoperative hematocrit (normal) ⩾ 36 mg/dL *vs* abnormal (< 36 mg/dL)], and surgery type [video-assisted thoracic surgery (VATS) *vs* open]. Baseline demographic and clinical

Table 2 Unadjusted intraoperative and postoperative complications

Characteristic	Total *n* = 4063	Neoadjuvant patients *n* = 236 (5.81%)	Surgery-only patients *n* = 3827 (94.19%)	*P*-value[1]
30-d mortality (%)	107 (2.63)	19 (8.05)	88 (2.30)	< 0.001[2]
Overall morbidity (%)	646 (15.90)	63 (26.69)	583 (15.23)	< 0.001[2]
Wound infection	4 (0.10)	0 (0.00)	4 (0.10)	0.787
Pneumonia	5 (0.73)	0 (0.00)	5 (0.77)	0.774
Urinary tract infection	1 (0.15)	0 (0.00)	1 (0.16)	0.956
Return to OR	201 (4.95)	22 (9.32)	179 (4.68)	< 0.001[2]
Venous thromboembolism	80 (1.97)	7 (2.97)	73 (1.91)	0.256
Cardiac complication	60 (1.48)	10 (4.24)	50 (1.31)	< 0.001[2]
Shock/sepsis	107 (2.63)	11 (4.66)	96 (2.51)	0.045[2]
Unplanned intubation	207 (5.09)	27 (11.44)	180 (4.70)	< 0.001[2]
Bleeding transfusion	178 (4.38)	28 (11.86)	150 (3.92)	<0.001[2]
Renal complication	22 (0.54)	0 (0.00)	22 (0.57)	0.636
On ventilator > 48 h	3 (0.07)	1 (0.42)	2 (0.05)	0.164
Organ space SSI	44 (1.08)	1 (0.42)	43 (1.12)	0.516
Serious morbidity (%)	469 (11.54)	44 (18.64)	425 (11.11)	< 0.001[2]
Length of stay (d), median (IQR)	6 (4-9)	6 (4-9)	6 (4-8)	0.915
Prolonged length of stay (%)	816 (20.08)	46 (19.49)	770 (20.12)	0.815
Operative time (min), median (IQR)	161 (123-216)	160 (121-214)	192 (147-250)	< 0.001[2]
Prolonged operative time (%)	1006 (24.76)	91 (38.56)	915 (23.91)	< 0.001[2]

[1]*P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]Two-sided values < 0.05 considered statistically significant. Wilcoxon rank-sum tests used to compare rank sum differences in non-normal distributions of length of stay and operative time. Overall morbidity: Wound infection, pneumonia, urinary tract infection, venous thromboembolism, bleeding transfusion, renal complication, return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Serious morbidity: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Prolonged length of stay and operative time refer to times longer than the 75th percentiles for the respective distributions; IQR: Interquartile range; SSI: Surgical site infection; OR: Operating room.

characteristics were compared between neo-adjuvant patients (receipt of chemotherapy and/or radiotherapy) and surgery-only patients (receipt of neither chemotherapy nor radiotherapy) using χ^2 tests (Fisher's exact test in cell counts less than five) for categorical variables. Two-sided *P*-values < 0.05 were considered statistically significant. To account for non-normal age distributions within the study population, Wilcoxon rank-sum tests were used to compare rank sum differences in age.

The primary outcome measure considered was 30-d postoperative mortality. Secondary intraoperative and postoperative outcomes measures included overall morbidity, serious morbidity, length of stay (LOS, days), prolonged LOS (defined as a LOS longer than the 75th percentile), operative time (min), and prolonged operative time (defined as an operative time longer than the 75th percentile). Overall morbidity was defined by presence of at least one of the following ACS-NSQIP complications: Wound infection [superficial or deep incisional surgical site infection (SSI), wound dehiscence], pneumonia, urinary tract infection (UTI), return to operating room (OR), venous thromboembolic event (VTE) (deep vein thrombosis/thrombophlebitis, pulmonary embolism), cardiac complication (cardiac arrest, myocardial infarction), shock/sepsis, unplanned intubation, bleeding requiring transfusion, renal complication (postoperative renal failure, progressive renal insufficiency), ventilator dependency > 48 h, or organ space SSI. Serious morbidity included occurrence of at least one of the following complications: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, ventilator dependency for > 48 h, or organ space SSI. As with baseline characteristics, outcome measures (Table 2) were compared between neo-adjuvant and surgery-only patients using χ^2 tests (Fisher's exact test in cell counts less than five) for categorical variables and Wilcoxon rank-sum tests to compare non-normal distributions of LOS and operative times.

Unadjusted and risk-adjusted odds ratios (and corresponding 95%CI) were calculated for differences in 30-d mortality, serious and overall morbidity, constituent morbidity measures, and prolonged LOS and operative time using (multivariable) logistic regression. Risk-adjusted models accounted for potential confounding due to significant differences in baseline factors: Age, smoking, hypertension, weight loss, steroid use, abnormal WBC count, abnormal hematocrit, and type of surgery performed. Colinearity/multicolinearity was assessed for adjusted models *via* calculation of variance inflation factors all well below a critical threshold of 10.0. For the continuous right-skewed distributions of LOS and operative time, modified Park tests were used to determine the most appropriate distribution (Poisson in both cases) to be used in a generalized linear model (link log). Average marginal effects were then used to calculate predicted differences in unadjusted and adjusted mean LOS (days) and operative time (min) in a manner analogous to that described for logistic regression (Table 3).

Finally, to more robustly corroborate the findings presented in Table 3 and to bolster the weight of the low

Table 3 Intraoperative/postoperative outcomes overall and among propensity-score matched cohorts (results represent odds ratios unless otherwise indicated)

Characteristic	Unadjusted (95%CI)	*P*-value[1]	Risk-adjusted (95%CI)	*P*-value[1]	Propensity-score matched cohort[3] (95%CI)	*P*-value[1]
30-d mortality (%)	3.72 (2.22-6.22)	< 0.001[1]	2.70 (1.54-4.72)	0.001[1]	1.63 (0.77-3.45)	0.197
Overall morbidity (%)	2.02 (1.50-2.74)	< 0.001[1]	1.53 (1.12-2.11)	0.010[1]	1.68 (1.08-2.62)	0.021[1]
Return to OR	2.09 (1.32-3.33)	0.001[1]	1.77 (1.08-2.90)	0.023[1]	3.37 (1.41-8.04)	0.006[1]
Cardiac complication	3.34 (1.67-6.70)	0.001[1]	3.11 (1.47-6.57)	0.003[1]	2.57 (0.79-8.30)	0.116
Shock/sepsis	1.90 (1.00-3.60)	0.049[1]	1.53 (0.78-3.02)	0.217	3.80 (1.05-13.80)	0.043[1]
Unplanned intubation	2.62 (1.71-4.02)	< 0.001[1]	2.03 (1.28-3.22)	0.002[1]	1.66 (0.88-3.14)	0.116
Bleeding transfusion	3.30 (3.15-5.06)	< 0.001[1]	1.72 (1.08-2.73)	0.023[1]	2.31 (1.17-4.58)	0.016[1]
Serious morbidity (%)	1.83 (1.30-2.58)	0.001[1]	1.55 (1.08-2.23)	0.018[1]	1.70 (1.02-2.85)	0.042[1]
Length of stay (d)[2]						
Predicted difference in means	-0.02 (-0.38 to 0.35)	0.927	-0.93 (-1.32 to -0.55)	< 0.001[1]	-1.02 (-1.54 to -0.50)	< 0.001[1]
Prolonged length of stay (%)	0.96 (0.87-1.34)	0.815	0.67 (0.47-0.96)	0.030[1]	0.63 (0.41-0.97)	0.037[1]
Operative time (min)[2]						
Predicted difference in means	30.5 (28.8-32.1)	< 0.001[1]	26.4 (24.7-28.1)	< 0.001[1]	29.0 (26.5-31.6)	< 0.001[1]
Prolonged operative time (%)	2.00 (1.52-2.62)	< 0.001[1]	1.81 (1.36-2.41)	< 0.001[1]	1.73 (1.17-2.57)	0.006[1]

[1]Two-sided *P*-values < 0.05 considered statistically significant. Adjusted models controlled for age, being a current smoker within one year, hypertension requiring medication, > 10% loss of body weight in last 6 mo, steroid use for chronic condition, abnormal preoperative WBC, abnormal preoperative hematocrit, abnormal preoperative albumin, operative year, managing specialty, and type of surgery preformed; [2]Modified Park tests corresponded to a Poisson distribution. Generalized linear models (family Poisson, link log) were used to model non-normally distributed continuous data, followed by post-estimation average marginal effects to attain predicted mean differences and 95%CI. Interpretation: Patients treated with neo-adjuvant therapy had average operative times that were longer than those of surgery-only patients by 29.0 min (95%CI: 26.5-31.6 min); [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for significant baseline differences in demographic and clinical characteristics. OR: Operating room.

percentage of neo-adjuvant patients observed (5.81%), rates of intraoperative and postoperative complications and corresponding adjusted odds ratios were calculated among separate cohorts generated for each outcome using propensity-score-based 1:1 nearest-neighboring matching without replacement, accounting for baseline differences in demographic and clinical factors. Within the calculated cohorts, logistic regression and modified Park tests/Poisson regression with average marginal effects were used as previously described.

Finally, in order to explore potential variations in outcomes between different neo-adjuvant regimens, a sub group analysis was performed (Tables 4-6). More specifically, outcomes of patients treated with surgery alone were compared to outcomes of patients who underwent surgical resection after neo-adjuvant chemotherapy alone, neo-adjuvant radiotherapy alone and neo-adjuvant chemo-radiotherapy. The methodology of this sub-group analysis closely reflects that of the primary analysis of the study, except for the fact that to account for non-normal age distributions within the study population, Kruskal-Wallis non-parametric one-way analysis of variance tests were used to compare rank sum differences in age. Moreover, additional variables, such as preoperative albumin level [normal (≥ 3.5 g/dL) *vs* abnormal (< 3.5 g/dL)] and managing surgical specialty (thoracic, general, other speciality) were accounted for.

All data analyses and management were performed using Stata/MP version 12 (StataCorp LP, College Station, TX, United States). The statistical review of the study was performed by a biomedical statistician.

RESULTS

We identified 4063 patients who had lung surgery from 2005 to 2012, and had information on pre-operative treatment. Induction treatment was given to 236 (5.8%) patients; of those, 64 underwent chemo-radiation, 103 radiation alone, 69 chemotherapy alone. The percentages of patients receiving induction, and the type of neo-adjuvant treatment used across the study years are shown in Figure 1. We compared the results to 3827 patients (94.2%) treated with upfront surgery. Demographic characteristics were significantly different between the two groups (Table 1). Patients who underwent induction treatment were younger (66 *vs* 69, $P < 0.001$), reported higher recent weight loss (6.8% *vs* 3.5%; $P = 0.011$), were active smokers (48.3 *vs* 34.9, $P < 0.001$), and had lower preoperative cell counts (abnormal WBC: 25.6 *vs* 13.4; $P < 0.001$; low hematocrit 53% *vs* 17.3%, $P < 0.001$). Furthermore, we observed significantly lower rates of VATS resections (14.41% *vs* 13.55%, $P < 0.001$) among neo-adjuvant patients. On unadjusted analysis, patients who received induction therapy had significantly higher 30-d mortality, overall and serious morbidity (Table 2). Odds of experiencing prolonged operative time and reoperation rates were also higher among patients in the neo-adjuvant group. Adjusted analysis showed similar findings: Patients who underwent induction had significantly higher mortality [odds ratio (OR), 2.70; 95%CI: 1.54-4.72; $P = 0.001$], overall (OR, 1.53; 95%CI: 1.12-2.11; $P = 0.010$) and serious (OR, 1.55; 95%CI: 1.08-2.23; $P = 0.018$) morbidity and higher odds of experiencing prolonged operative time (OR, 1.81; 95%CI:

Table 4 Baseline demographic and clinical characteristics among the unmatched population cohort

Characteristic	Surgery only *n* = 3593 (94.21%)	Chemotherapy *n* = 64 (1.68%)	Radiotherapy *n* = 100 (2.62%)	Chemo and radio *n* = 57 (1.49%)	*P*-value[1]
Age (yr), median (IQR)	69 (61-75)	66 (62-73)	66 (53-69)	62 (52-70)	< 0.001[2]
Male (%)	1774 (49.59)	35 (54.69)	45 (45.45)	28 (49.12)	0.662
Race (%)					
Non-Hispanic White	2678 (78.58)	48 (78.69)	83 (86.46)	46 (85.19)	0.508
Non-Hispanic Black	194 (5.69)	3 (4.92)	5 (5.21)	4 (7.41)	
Hispanic	393 (11.53)	7 (11.48)	4 (4.17)	3 (5.56)	
Other or unknown	143 (4.20)	3 (4.92)	4 (4.17)	1 (1.85)	
ASA classification (%)					
1-2 no-mild disturbance	2573 (71.61)	51 (79.69)	71 (71.00)	41 (71.93)	0.445
3 serious disturbance	665 (18.51)	10 (15.63)	19 (19.00)	7 (12.28)	
4-5 life threatening/moribund	355 (9.88)	3 (4.69)	10 (10.00)	9 (15.79)	
Functional status					
Independent	3528 (98.19)	61 (95.31)	98 (98.00)	56 (98.25)	0.413
Partially/totally dependent	65 (1.81)	3 (4.69)	2 (2.00)	1 (1.75)	
Obese, BMI ⩾ 30 (%)	1093 (30.42)	20 (31.25)	22 (22.00)	14 (24.56)	0.245
Diabetes (%)	546 (15.20)	11 (17.19)	9 (9.00)	5 (8.77)	0.178
Current smoker (%)	1223 (34.04)	29 (45.31)	48 (48.00)	30 (52.63)	< 0.001[2]
Alcohol consumption (%)	193 (5.37)	5 (7.81)	6 (6.00)	4 (7.02)	0.785
Dyspnea (%)	975 (27.14)	14 (21.88)	24 (24.00)	16 (28.07)	0.711
History of COPD (%)	962 (26.77)	19 (29.69)	21 (21.00)	11 (19.30)	0.317
History of heart disease (%)	38 (1.06)	0 (0.00)	3 (3.00)	0 (0.00)	0.186
Hypertension (%)	2134 (59.39)	31 (48.44)	48 (48.00)	25 (43.86)	0.004[2]
Previous cardiac surgery (%)	280 (7.79)	2 (3.13)	6 (6.00)	3 (5.26)	0.422
Weight loss (%)	115 (3.20)	0 (0.00)	8 (8.00)	5 (8.77)	0.003[2]
Steroid use (%)	132 (3.67)	6 (9.38)	10 (10.00)	3 (5.26)	0.001[2]
Year of operation (%)					
2005-2008	728 (20.26)	6 (9.38)	34 (34.00)	9 (15.79)	< 0.001[2]
2009-2010	1577 (43.89)	21 (32.81)	61 (61.00)	18 (31.58)	
2011-2012	1288 (35.85)	37 (57.81)	5 (5.00)	30 (52.63)	
Preoperative WBC (%)					
Normal (4.5-11.0 × 10^9/L)	2988 (83.16)	54 (84.38)	73 (73.00)	38 (66.67)	< 0.001[2]
Abnormal (< 4.5 or > 11.0 × 10^9/L)	468 (13.03)	10 (15.63)	27 (27.00)	17 (29.82)	
Preoperative hematocrit (%)					
Normal (⩾ 36)	2860 (79.60)	32 (50.00)	52 (52.00)	23 (40.35)	< 0.001[2]
Abnormal (< 36)	588 (16.37)	32 (50.00)	48 (48.00)	32 (56.14)	
Preoperative albumin (%)					
Normal (⩾ 3.5 g/dL)	3345 (93.10)	58 (90.63)	82 (82.00)	55 (96.49)	< 0.001[2]
Abnormal (< 3.5 g/dL)	248 (6.90)	6 (9.38)	18 (18.00)	2 (3.51)	
Managing specialty (%)					
Thoracic	2243 (62.43)	48 (75.00)	48 (48.00)	40 (70.18)	0.008[2]
General	991 (27.58)	11 (17.19)	42 (42.00)	11 (19.30)	
Other specialty	359 (9.99)	5 (7.81)	10 (10.00)	6 (10.53)	
Surgery type (%)					
Open	2545 (70.83)	51 (79.69)	86 (86.00)	53 (92.28)	< 0.001[2]
VATS	1048 (29.17)	13 (20.31)	14 (14.00)	4 (7.02)	

[1]Two-sided *P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]*P*< 0.05 considered statistically significant. Kruskal-Wallis one-way analysis of variance was used to compare non-normal distributions of age. ASA: American Society of Anesthesiology; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; MI: Myocardial infarction; WBC: White blood cell (count); VATS: Video-assisted thoracic surgery; BMI: Body mass index; IQR: Interquartile range.

1.36-2.41; *P* < 0.001) (Table 3). Interestingly, patients treated with surgery alone had higher LOS and prolonged LOS.

Results after matching for baseline differences in demographic and clinical factors are shown in Table 7. While differences in mortality among the groups were non-significant, overall morbidity, serious morbidity and prolonged operative time remained higher in the neo-adjuvant group.

Results of the sub-group analysis comparing outcomes of surgery alone to those of different neo-adjuvant regimens did not show clinically meaningful differences between the neo-adjuvant sub groups (Tables 4-6).

DISCUSSION

The results from our analysis demonstrated globally worse postoperative outcomes in patients who received neo-adjuvant treatment before lung resection, when compared to those treated with surgery alone. Thirty-day overall and serious morbidity rates as well as operative times, were consistently higher in patients receiving induction treatment. Conversely, higher mortality in the neo-adjuvant group was statistically

Table 5 Unadjusted intraoperative/postoperative outcomes among the unmatched population cohort

Characteristic	Surgery only *n* = 3593 (94.21%)	Chemotherapy *n* = 64 (1.68%)	Radiotherapy *n* = 100 (2.62%)	Chemo and radio *n* = 57 (1.49%)	*P*-value[1]
30-d mortality (%)	83 (2.31)	3 (4.69)	9 (9.00)	5 (8.77)	< 0.001[2]
Overall morbidity (%)	415 (11.55)	13 (20.31)	21 (21.00)	17 (29.82)	< 0.001[2]
Wound infection	3 (0.08)	0 (0.00)	0 (0.00)	0 (0.00)	--
Pneumonia	4 (0.11)	0 (0.00)	0 (0.00)	0 (0.00)	--
Urinary tract infection	1 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	--
Return to OR	170 (4.73)	7 (10.94)	10 (10.00)	4 (7.02)	0.012[2]
Venous thromboembolism	70 (1.95)	0 (0.00)	2 (2.00)	3 (5.26)	0.212
Cardiac complication	47 (1.31)	2 (3.13)	2 (2.00)	4 (7.02)	0.002[2]
Shock/sepsis	92 (2.62)	2 (3.13)	5 (5.00)	2 (3.51)	0.513
Unplanned intubation	169 (4.70)	5 (7.81)	12 (12.00)	7 (12.28)	< 0.001[2]
Bleeding transfusion	133 (3.70)	8 (12.50)	7 (7.00)	10 (17.54)	< 0.001[2]
Renal complication	22 (0.61)	0 (0.00)	0 (0.00)	0 (0.00)	--
On ventilator > 48 h	2 (0.06)	1 (1.56)	0 (0.00)	0 (0.00)	--
Organ space SSI	38 (1.06)	0 (0.00)	1 (1.00)	0 (0.00)	--
Serious morbidity (%)	372 (10.35)	12 (18.75)	19 (19.00)	10 (17.54)	0.002[2]
Length of stay (d), median (IQR)	6 (4-8)	5 (4-7)	6 (5-9)	5 (4-8)	0.134
Prolonged length of stay (%)	899 (25.02)	10 (15.63)	28 (28.00)	13 (22.81)	0.306
Operative time (min), median (IQR)	160 (121-214)	187 (140-246)	202 (151-253)	182 (142-249)	< 0.001[2]
Prolonged operative time (%)	858 (23.44)	23 (35.94)	41 (41.00)	20 (35.09)	< 0.001[2]

[1]Two-sided *P*-values taken from χ^2 tests (Fisher's exact test in cell counts less than five); [2]$P < 0.05$ considered statistically significant. Kruskal-Wallis one-way analysis of variance was used to compare non-normal distributions of length of stay and operative time. Overall morbidity: Wound infection, pneumonia, urinary tract infection, venous thromboembolism, bleeding transfusion, renal complication, return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Serious morbidity: Return to OR, cardiac complication, shock/sepsis, unplanned intubation, on ventilator > 48 h, and organ space SSI. Prolonged length of stay, prolonged operative time refers to times longer than the 75th percentiles for the respective distributions. OR: Operating room; SSI: Surgical site infection; IQR: Interquartile range.

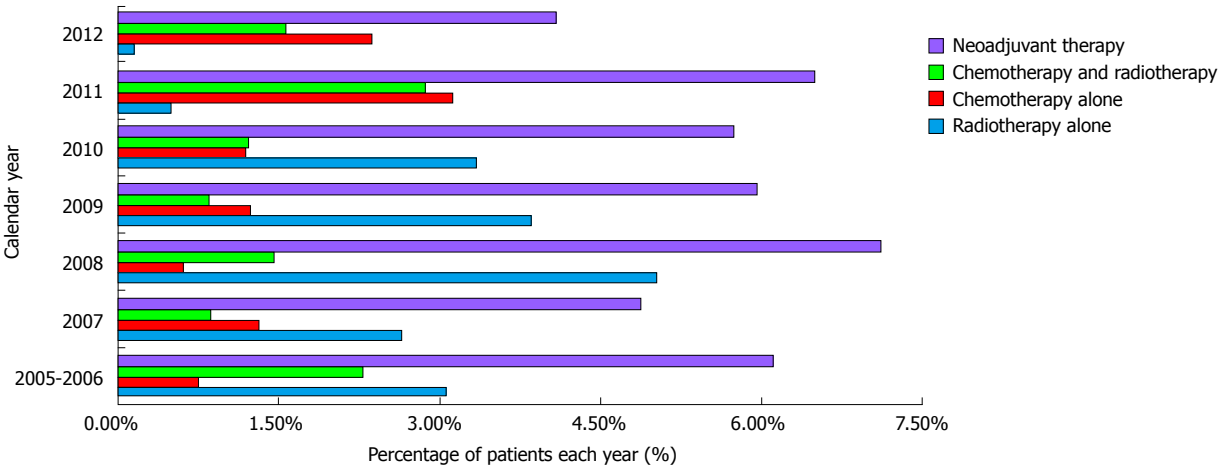

Figure 1 Percentage of patients receiving neo-adjuvant therapy across the study years. The denominations "chemotherapy alone" and "radiotherapy alone" indicate patients who underwent surgery after respectively neo-adjuvant chemotherapy not associated with neo-adjuvant radiotherapy, and neo-adjuvant radiotherapy not associated with neo-adjuvant chemotherapy.

non-significant after matching.

The two groups showed several differences at baseline, some of which likely reflected the effects of neo-adjuvant administration. Patients in the induction group, in fact, demonstrated signs of malnutrition and myelosuppression, as shown by their weight loss and lower blood cell counts. Likewise, probably some patients' characteristics such as more advanced age influenced the decision to avoid neo-adjuvant treatment.

In our population, a significantly higher percentage of patients in the neo-adjuvant group were current smokers, as defined by NSQIP (the patient has smoked cigarettes in the year prior to admission for surgery). It has been reported that continued smoking after cancer diagnosis was related to reduced treatment efficacy, increased treatment-related complications and reduced survival[11]. Even though this could have partially influenced the induction group's worse results, it is worth stressing that most differences in post-operative adverse events persisted after adjusting for smoking habits. Chronic steroid use, which was more prevalent among patients who received neo-adjuvant therapy, is

Table 6 Intraoperative/postoperative outcomes among propensity-score matched cohorts[3] relative to the surgery only group (results represent odds ratios unless otherwise indicated)

Characteristic	Surgery only varied size with cohort	Chemotherapy *n* = 64 matched patients	Radiotherapy *n* = 100 matched patients	Chemo and radio *n* = 57 matched patients
30-d mortality (%)	1.00 (reference)	0.74 (0.16-3.43)	1.24 (0.73-2.13)	1.38 (0.79-2.43)
Overall morbidity (%)	1.00 (reference)	1.10 (0.46-2.65)	1.14 (0.80-1.62)	1.38 (1.01-1.89)[1]
Serious morbidity (%)	1.00 (reference)	1.25 (0.50-3.13)	1.00 (0.70-1.42)	1.00 (0.72-1.38)
Length of stay (d)[2]				
Predicted mean difference	0.00 (reference)	-1.43 (-2.19 to -0.68)[1]	0.34 (0.08-0.60)[1]	-0.04 (-0.28-0.21)
Prolonged length of stay (%)	1.00 (reference)	0.56 (0.21-1.46)	0.95 (0.68-1.31)	0.78 (0.57-1.06)
Operative time (min)[2]				
Predicted mean difference	0.00 (reference)	13.8 (10.7-17.0)[1]	19.9 (18.7-21.1)[1]	9.49 (8.41-10.6)[1]
Prolonged operative time (%)	1.00 (reference)	2.20 (1.00-4.87)[1]	1.56 (1.15-2.11)[1]	1.03 (0.79-1.34)

[1]Two-sided *P*-values < 0.05 considered statistically significant; [2]Modified Park tests corresponded to a Poisson distribution. Generalized linear models (family Poisson, link log) were used to model non-normally distributed continuous data, followed by post-estimation average marginal effects to attain predicted mean differences and 95%CI. Interpretation: Patients treated with chemotherapy had average operative times that were longer than those of surgery-only patients by 13.8 min (95%CI: 10.7-17.0); [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for significant baseline differences in demographic and clinical characteristics.

Table 7 Rates of intraoperative and postoperative complications in cohorts matched for each outcome

Characteristic	Neoadjuvant patients *n* = 234 (50.00%)[3]	Surgery-only patients *n* = 234 (50.00%)[3]	Odds ratio (95%CI)	*P*-value[1]
30-d mortality (%)	19 (8.12)	12 (5.13)	1.63 (0.77-3.45)	0.197
Overall morbidity (%)	63 (26.92)	42 (17.95)	1.68 (1.08-2.62)	0.021[1]
Return to OR	22 (9.40)	7 (2.99)	3.37 (1.41-8.04)	0.006[1]
Cardiac complication	10 (4.27)	4 (1.71)	2.57 (0.79-8.30)	0.116
Shock/sepsis	11 (4.70)	3 (1.28)	3.80 (1.05-13.80)	0.043[1]
Unplanned intubation	27 (11.54)	17 (7.26)	1.66 (0.88-3.14)	0.116
Bleeding transfusion	28 (11.97)	13 (5.56)	2.31 (1.17-4.58)	0.016[1]
Serious morbidity (%)	44 (18.80)	28 (11.97)	1.70 (1.02-2.85)	0.042[1]
Length of stay (d)[2]				
Predicted difference in means	--	--	-1.02 (-1.54 to -0.50)	< 0.001[1]
Prolonged length of stay (%)	44 (18.80)	63 (26.92)	0.63 (0.41-0.97)	0.037[1]
Operative time (min)[2]				
Predicted difference in means	--	--	29.0 (26.5-31.6)	< 0.001[1]
Prolonged operative time (%)	90 (38.46)	62 (26.50)	1.73 (1.17-2.57)	0.006[1]

[1]Two-sided values < 0.05 considered statistically significant; [2]Modified Park test found Poisson most appropriate distribution to account for non-normality of the count data; average marginal effects used to calculate predicted difference in the mean; [3]Separate cohorts were generated for each outcome using propensity-score-based 1:1 nearest-neighbor matching without replacement, accounting for baseline differences in demographic and clinical characteristics. While all cohorts had an equal distribution of matched neoadjuvant and surgery-only patients (*n* = 234) by design, no two cohorts necessarily contain the same patients in order to account for cohorts appropriately weighted to each outcome. OR: Operating room.

another factor that has previously been associated with worse surgical outcomes[12]. Of note, the higher rates of steroid use observed in the induction group could in part represent therapy for drug- and radiation-induced pulmonary toxicity, which is routinely treated with high dose of steroids[13,14]. Yet, only prolonged steroid treatment would meet the requirements to be collected by the NSQIP under the "steroid" variable.

The occurrence of some of the adverse events observed more frequently in the induction group can be directly related to neo-adjuvant therapy. Thrombocytopenia induced by myelotoxic drugs, for example, might worsen bleeding risk, regardless the chemotherapy used[15]. Similarly, lower leukocyte counts can certainly predispose to the development of sepsis. Moreover, some authors have expressed concern that induction therapy may promote pleural adhesion and vascular fragility, resulting in anatomic disruptions detrimental for surgical outcomes[5]. Analogously, radiation-induced fibrosis can result in a more complex-hence prone to structural damage-dissection between the anatomical planes, which can easily account for lengthier operative times and higher bleeding rates, as observed in the neo-adjuvant patients. Of note, in the NSQIP database the "postoperative bleeding" variable is recorded by using the number of transfusions given as a surrogate; since patients who received induction treatment had a higher chance for myelosuppression, they intuitively had higher probability of developing a significant postoperative anemia requiring transfusion.

On adjusted analysis, patients who underwent neo-adjuvant therapy appeared to have shorter LOS and reduced odds of experiencing prolonged LOS than patients treated with surgery alone; this is counterintuitive, give the globally worse outcomes of the induction group. Nevertheless it is worth recalling that the NSQIP variable "discharge destination" was included in 2011. Understanding the destination after discharge is important to evaluate if the LOS for neo-adjuvant patients was actually shorter due to early discharge home or an artifact attributable to a transfer to another facility.

Several different protocols of neo-adjuvant therapy have been designed and tested for lung cancer, and their overall benefit varies according to tumor stage and type of induction used. Results of a recent systematic review and meta-analysis of randomized controlled trials, showed that patients affected by non-small-cell lung cancer who underwent preoperative chemotherapy had significantly improved overall survival, time to distant recurrence, and recurrence-free survival in resectable non small cell lung cancer (NSCLC)[16]. Analysis of data from the National Cancer Database suggested that neo-adjuvant chemo-radiation followed by lobectomy, was associated with an improved survival in patients with advanced NSCLC[17]. A large randomized trial showed that the addition of pre-operative chemo-radiation to chemotherapy, in patients with resectable stage Ⅲ NSCLC increases pathological response and mediastinal downstaging, without however affecting survival[18]. The same study showed a remarkable increased in treatment-related mortality in patients who underwent pneumonectomy after having received chemo-radiation, to the point that the risk outweighed the benefit of therapy. Shah *et al*[19] reported that the addition of induction radiotherapy to induction regimens granted no benefit in survival and discouraged its routinely use, given the potential harmful effects of radiation itself. On the other hand, Toyooka *et al*[20] indeed suggested that induction chemo-radiotherapy could be superior to induction chemotherapy alone in selected groups of patients, such as those with mediastinal lymph node metastasis. There are fewer studies on the use of neo-adjuvant therapy for early stage lung cancer; some data have suggested potential advantages of induction, showing a trend towards better survival, which, however, did not reach statistical significance[21]. Even though the NSQIP database does not allow us to study oncologic outcomes, it still provides valuable and reliable information about surgical outcomes. The assessment of mortality and morbidity in patients undergoing neo-adjuvant therapy for lung cancer is timely and relevant, given the concerns raised by the potential harms of induction protocols. Several authors have described increased post-operative adverse events after neo-adjuvant therapy, with global complication rates as high as 43.5% in patients who underwent chemo-radiotherapy[22]. Our results correlate well with the STS database analysis performed by Kozower *et al*[23]. These authors developed a large risk model for morbidity and mortality after lobectomy, sleeve lobectomy, bilobectomy, pneumonectomy, segmentectomy, and wedge resection for primary lung cancer, and observed that induction chemo-radiation therapy is an independent predictor of mortality and major morbidity. However, our work also showed some interesting differences from similar studies in the literature. Evans *et al*[8] queried the STS General Thoracic Surgery Database in order to examine outcomes of patients undergoing lung resections after neo-adjuvant treatment. According to their analysis, induction therapy did not increase the odds of discharge mortality, prolonged LOS, or major morbidity. Several differences, which may account for this discrepancy in results, are worth being stressed. First of all Evans *et al*[8] only focused on major resections, such as lobectomies and pneumonectomies. Secondarily, our two studies present some differences in the types of statistical analysis chosen, as well as in the morbidities selected as outcomes. Finally, it is important to recall that NSQIP has the potential of capturing more data from general surgery units than STS, which is more specialty-oriented. Our data, in fact, showed that almost 40% of the pulmonary resection in our study where not performed by thoracic surgeons (Table 4). It is indeed known that general surgeons perform the majority of lung resections in the United States (more than 50%), even though they have on average significantly lower median thoracic surgical procedure case volumes compared with general thoracic and cardiac surgeons[24]. In parallel, it has been reported that thoracic surgeons, in high-volume personal and hospital settings, achieve the best outcomes for lung resections[25]. As a consequence, it is reasonable to postulate that also differences in the distribution of surgeons' specializations across the two datasets might be one of the underlying causes of the observed discrepancies in outcomes.

Our study has several limitations in part related to the type of dataset used. NSQIP in fact, collects data only for 30 and 90 d before surgery for chemotherapy and radiation therapy respectively. Therefore if a patient received any treatment before this period of time, the patient could have been mislabeled as never receiving treatment at all. Moreover all patients without information regarding induction therapy were excluded from the study. Also, patients who were not surgical candidate due to unexpected complications of induction therapy were not recorded in this dataset and therefore excluded from this study. Information about drugs type and dosage as well a radiation planning were not available to us to optimize our analysis. Furthermore, in order to achieve greater statistical power, we grouped different neo-adjuvant regimens together under the broader group of "surgery following neo-adjuvant therapy". While this approach necessarily leads to some loss of insight within the single neo-adjuvant regimens, we believe that it was appropriate for the purpose of the present study; in fact it is worth stressing that our sub-group analysis did not show clinically meaningful differences among the various neo-adjuvant sub-groups. Patients' baseline

and tumor's characteristics (including stage) might have influenced the decision to give induction therapy. NSQIP however does not provide this information and therefore we can't comment on the indication for neo-adjuvant therapy. We found significantly more open cases in the induction group, yet, it is not possible to determine if those procedures started as open procedures or were conversions from VATS, since both these events are recorded as open in NSQIP. In addition only few hospitals voluntarily participate in the NSQIP database and therefore our results might not apply to all hospitals and the general population. Finally, this database records data only for 30 d after surgery and a longer follow-up cannot be evaluated, especially in regards to oncologic results.

Although with some limitations, our study shows important results to consider when treating a patient with lung cancer who underwent induction therapy.

This study shows that induction treatment for lung cancer leads to worse early post-operative outcomes after lung resection. Further research will be necessary in order to individuate subgroups of patients particularly susceptible to develop complications. With these assumptions, since the evidence in favor of neo-adjuvant therapy for lung cancer is not as compelling as for other cancers, we believe that the indication for induction should be weighted carefully for every patient against its possible downsides, in order to exploit its benefits while minimizing the potential harm.

COMMENTS

Background

Induction therapy for lung cancer has been reported to modestly improve survival in locally advanced disease. However, the impact of treatment on surgical outcomes has not been extensively studied.

Research frontiers

In an attempt to improve survival for this disease, several multimodality treatment approaches, including neo-adjuvant therapy protocols, have been developed through the years. The concern of developing life-threatening complications, prevalent and severe enough to offset the potential benefits of induction, can constitute a significant obstacle for the diffusion of neo-adjuvant protocols.

Innovations and breakthroughs

In this study, results showed globally worse postoperative outcomes in patients who underwent neo-adjuvant therapy prior to lung resection, when compared to those treated with surgery alone.

Applications

Indication for induction therapy should be weighted carefully for every patient against its possible downsides, in order to exploit its benefits while minimizing the potential harm.

Terminology

American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) is a large, nationally-validated, risk-adjusted, outcomes-based program used to measure and improve the quality of surgical care.

Peer-review

Well-prepared and discussed review on affects of treatment and/or surgery of lung cancer. While it is hard to believe that similar studies were not performed in past, particularly considering the wide occurrence of this type of tumor, the results are interesting and clinically important.

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MINIREVIEWS

Glycemic management in critically ill patients

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Abstract

Hyperglycemia associated with critical illness, also called "stress hyperglycemia" or "stress diabetes", is a consequence of many pathophysiologic hormonal responses including increased catecholamines, cortisol, glucagon, and growth hormone. Alterations in multiple biochemical pathways result in increased hepatic and peripheral insulin resistance with an uncontrolled activation of gluconeogenesis and glycogenolysis. Hyperglycemia has a negative impact on the function of the immune system, on the host response to illness or injury, and on infectious and overall outcomes. The degree of glucose elevation is associated with increased disease severity. Large randomized controlled trials including the Van den Berghe study, the NICE-SUGAR trial, VISEP and GLUCONTROL have shown that the control of glucose levels in critically ill patients has implications on outcome and that both hyperglycemia and hypoglycemia are detrimental and should be avoided. Glucose variability has also been shown to be detrimental. Aggressive glucose control strategies have changed due to the concerns of hypoglycemia and therefore intermediate target glucose control strategies are most often adopted. Different patient populations may vary with regards to optimal glucose targets, timing and approach for glucose control, and with regards to the prognostic significance of glucose excursions and variability. Medical, surgical, and trauma patients may benefit at different rates from glucose control and the approach may need to be adapted to various medical settings and to correspond to the workflow of health providers. Effect modifiers for the success of insulin therapy for hyperglycemia include the methods of nutritional supplementation and exogenous glucose administration. Further research is required to improve insulin protocols for glucose control, to further define glucose targets, and to enhance the accuracy of glucose measuring technologies.

Key words: Hyperglycemia; Hypoglycemia; Critically ill; Intensive care unit; Glucose control

Core tip: Hyperglycemia is not innocuous, especially in the critically ill; and glucose control has been shown to significantly impact morbidity and mortality. In this review, we describe the pathophysiology of the "diabetes

of stress"; we summarize the major investigations that constitute the body of evidence and the reasons behind current practices. Further, we emphasize glucose considerations in special populations, especially trauma and postoperative populations. Finally, we provide insight on the relative importance of avoiding hyperglycemia, hypoglycemia, and glucose variability.

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INTRODUCTION

Historically, elevation in blood glucose has been considered to be a compensatory response that exemplifies the metabolic changes required to cope with injury or illness. This view has radically changed since the seminal study by Van den Berghe *et al*[1] in the early 2000s. Glycemic control has been shown to have an important impact on outcome, especially in critically ill patients. Relevant glucose derangements include hyperglycemia, glycemic variability, and hypoglycemia. The ideal target for glucose control continues to be under debate. In this review, we will discuss the evidence behind current practices of glucose control with emphasis on glucose considerations in special populations, such as trauma and postoperative patients. We will also summarize the pathophysiology of hyperglycemia in the critically ill.

HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

Hyperglycemia is defined as an acute sustained rise in serum glucose levels[1]. Stress hyperglycemia is associated with the physiologic response to stress, including illness or injury. It is a multifactorial occurrence resulting from multiple metabolic derangements as well as the effects of medical treatments. Hyperglycemia is not innocuous; it incurs a range of adverse events, including abnormal immune function, increased infection rate, and hemodynamic and electromyocardial disturbances[2-6]. It is associated with increased insulin resistance and is partially due to the patient's inability to meet the increase in insulin demands that accompanies the metabolic stress response[3,6]. The clinical impact of hyperglycemia has been investigated in large clinical trials.

The landmark study by Van den Berghe *et al*[1] conducted in Leuven, Belgium, is a randomized interventional trial that enrolled 1548 patients admitted to a single intensive care unit (ICU) with a predominantly surgical population. In that study, intensive insulin therapy (IIT, target glucose range 80 to 110 mg/dL achieved by a titratable infusion of fast-acting insulin) resulted in a reduction in overall mortality of 32% compared to conventional glucose therapy (CGT, target glucose range 180 to 200 mg/dL, with insulin infusion only started at > 215 mg/dL). Furthermore, in this study, IIT decreased blood stream infections by 46%, acute renal dialysis requiring dialysis or hemofiltration by 41%, and transfusion requirements by 50%. The greatest reduction in mortality involved deaths due to multiple-organ failure with a septic focus, and involved long-stay patients defined as being in ICU for more than 5 d. The study was stopped early for safety reasons since CGT was inferior. Hypoglycemia occurred in 5.1% in IIT compared to 0.8% in CGT.

The Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) trial[7] was a multi-centered randomized interventional trial that was designed to address whether the benefit of IIT is generalizable to critically ill patients in general. The study was multi-centered and included 6104 patients of a mixed population of medical and surgical patients. Only patients expected to require ICU treatment for 3 or more days were enrolled. The results were opposite to the landmark study by Van den Berghe *et al*[1]. IIT (target glucose range 81 to 108 mg/dL) increased the risk of death by 2.6% compared to CGT (target glucose 180 mg/dL or less). The rate of hypoglycemia was 6.8% in IIT compared to 0.5% in CGT group. Interestingly, however, these results did not apply to the trauma subgroup in this study. The trauma subgroup of this study consisted of 886 patients. These patients were analyzed separately and a trend for decreased likelihood of death with IIT was found in this trauma subgroup.

Other studies aimed at determining the optimal target for blood glucose in the overall intensive care population. GLUCONTROL[8] was a multi-centered randomized interventional trial comparing IIT (target glucose range 79 to 110 mg/dL) and an intermediate glucose control (IGT, target glucose range 126-180 mg/dL). A total of 1078 patients were analyzed. The study was stopped prematurely because a high proportion of glucose values were outside the predetermined groups for the study. The study did not show a benefit for IIT. There was an increased rate of hypoglycemia in IIT (8.7% *vs* 2.7%). VISEP[9] (Volume Substitution and Insulin Therapy in severe Sepsis) trial, was a multicenter two-by-two factorial trial that randomized patients with severe sepsis to receive IIT (target glucose range 80 to 110 mg/dL) or CGT (target glucose range 180 to 200 mg/dL) and either 10% pentastarch or lactate ringer. The IIT arm was stopped first, after the inclusion of 537 patients, because of an increased rate of hypoglycemia (12.1% *vs* 2.1%). There was no significant difference in mortality, morbidity, or rate of organ failure between IIT and CGT.

A second Leuven study by Van den Berghe *et al*[10] was conducted in a medical ICU setting with the same glucose targets as the initial trial and found a reduced morbidity and length of stay with IIT but no effect on mortality among the 1200 patients. However, there was a reduction in mortality in the subgroup of patients

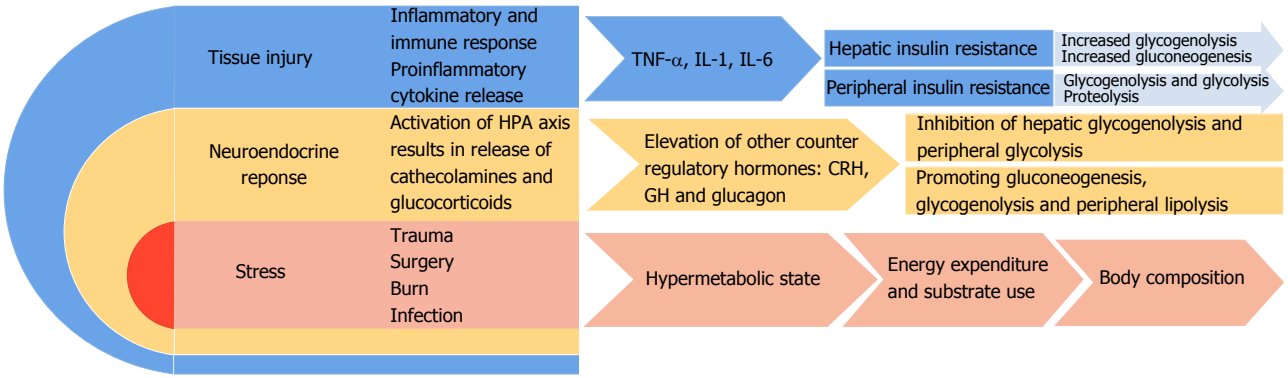

Figure 1 Response to metabolic stress. The metabolic homeostasis is affected once a stressor is identified. The response involves a series of neuroendocrine activations/inactivations and an inflammatory/immune component. The neuroendocrine response involves the activation of the hypothalamic-pituitary-adrenal axis resulting in an elevation of catecholamines and cortisol[73]. Other counter-regulatory hormones found also elevated during physiologic stress are CRH, GH and glucagon. These hormones inhibit hepatic glycogenesis and peripheral glycolysis while activating gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis[11]. The presence of glucagon activates the hepatic pathways of glycogenolysis and gluconeogenesis. Increased gluconeogenesis fueled by proteolytic, lipolytic, and glucolytic metabolites combined with hepatic insulin resistance are considered the main causes of stress-induced hyperglycemia, but more obvious factors such as exogenous dextrose, enteral or total parenteral nutrition, and simple bed rest can further aggravate this picture[11]. TNFα: Tumor necrosis factor α; IL: Interleukin; GH: Growth Hormone; CRH: Corticotrophin.

remaining more than 3 d in ICU by a subgroup analysis. The rate of hypoglycemia in this study is elevated, 3.1% in CGT compared to 18.7% in IIT.

A direct comparison between the initial Leuven[1] study and NICE-SUGAR[7] is difficult due to important differences in the target blood glucose and in the patient population. Reducing hyperglycemia incurs an increased rate of hypoglycemia, to varying degrees. Furthermore, there are significant treatment differences in these patients, such as enteral *vs* parenteral feeding and the instruments of glucose measurement. The reasons for these discrepancies in results are thus numerous. Some important qualifiers for the effect of glucose control in critically ill patients, will be addressed in depth in this review.

PATHOPHYSIOLOGY OF HYPERGLYCEMIA IN CRITICAL ILLNESS

The metabolic response to stress

Critically ill patients commonly enter a hypermetabolic state with distinct alterations in carbohydrate, protein, and lipid metabolism as part of the physiologic stress response. The pathways involved in the metabolic response are depicted in Figure 1. The magnitude of the metabolic response is proportional to the severity of injury. These effects are mediated by hormonal and neuroendocrine components as well as by cytokines released locally in response to injury.

The stress response involves the activation of the sympathoadrenal and hypothalamopituitary-adrenal axis, resulting in increased levels of catecholamines and glucocorticoids[11]. The effects of catecholamines include the increase in glycogenolysis in the liver and muscle and in peripheral lipolysis, which increases glucose and lactate[11,12]. Glucocorticoids increase glucose by similar mechanisms as well as by inhibiting glucose uptake and contributing to insulin resistance[11]. Sympathetic stimulation of the pancreas leads to an increase in glucagon secretion and a decrease in insulin secretion[13]. Insulin production is low in comparison to the level of glucose associated with the state of physiological stress.

Growth hormone, corticotropin, and glucagon are elevated in response to stress[12]. These hormones are counter-regulatory to insulin; they increase glucose levels in blood by increasing gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis while inhibiting hepatic glycogenesis[11]. The breakdown of glycogen, lipids, and muscle protein provide the substrates for hepatic gluconeogenesis, further increasing blood glucose in the critically ill[14,15]. Furthermore, pro-inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 (IL-6) can contribute to the state of peripheral and hepatic insulin resistance[16-18].

Glucose transport is altered in critical illness. There is usually a net rise in serum glucose levels in spite of the increase in glucose uptake[11,15,19]. The overall picture is that of an increased supply of substrates due to the catabolic state, as well as insulin resistance and relative insulin deficiency. There is a threefold lower intestinal absorption of glucose in the gut in the setting of critical illness[20,21], indicating that there is a homeostatic drive against hyperglycemia in critical illness. However, inflammatory cytokines, such as endothelin-1, transforming growth factor-beta, and tissue hypoxia increase the insulin-independent transport of glucose into various tissues, including neurons[22-24]. This provides needed energy for tissue repair regeneration; however, it also exposes these cells to the untoward effects of hyperglycemia.

Insulin resistance and compensatory mechanisms

Insulin resistance culminates in the inability to stimulate glucose uptake, mainly into skeletal muscle, or to inhibit gluconeogenesis in the liver. Insulin resistance mainly occurs *via* the intracellular signaling pathway

involving the insulin receptor/insulin-receptor substrates/phosphatidylinositol 3-kinase/Akt through a loss of insulin-mediated phosphorylation[25]. Insulin regulation of the hepatic pathway, Ras/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase, is less affected[25]. There is the added problem of increased substrates available for gluconeogenesis due to catabolism and the effect of counter-regulatory hormones as previously described. This issue is potentially compounded by the iatrogenic doses of glucose contained in therapeutic medications or treatments.

The development of insulin resistance is not a uniform process across disease processes or tissue types. Animal studies suggest that there are tissue-specific differences in the development of insulin resistance following injury[25]. Furthermore, the effect of a combination of trauma and hemorrhage in skeletal muscle with regards to insulin responsiveness, appears to occur by a distinct mechanism that is poorly understood. Trauma alone causes less insulin resistance than the combination of trauma and hemorrhage[25]. Glucagon has been shown to be a major factor in the development of hyperglycemia in burn patients. Add to this that there are individual-based variations in the degree of insulin resistance in the patient population.

In humans, glucose transporter channel protein-4 (GLUT-4) is specifically and reversibly upregulated by insulin[26] by the mechanism described above. The failure of this mechanism leads to decreased glucose uptake into skeletal muscle and adipose. GLUT-1 and GLUT-3, however, are basally active, and the concentration dependent increase in uptake due to hyperglycemia, leads to higher intracellular concentrations of glucose in glucose-sensitive tissues such as neurons and endothelial cells[26]. On the other hand, GLUT-2 which is responsible for glucose transport across the intestinal wall is downregulated in critical illness, which affords some systemic protection against the exacerbation of hyperglycemia in illness by intestinal uptake[20,21]. This is a protective mechanism that must be recognized in the setting of insulin-therapy.

Immune and inflammatory effects of hyperglycemia

Injury and acute illness, including states of shock, cardiac arrest, and acute respiratory distress, are associated with increased oxidative stress. The magnitude of the oxidative stress and the severity of the condition[27,28]. Acute inflammation, ischaemia-reperfusion, hypoxia, and hyperoxia, all involved in the state of acute injury or illness and its treatment, further enhance this imbalance between reactive oxygen species and anti-oxidants[29]. Oxidative stress increases the inflammatory response, which further increases the production of ROS like a vicious circle, and the resultant imbalance causes severe damage on essential structures such as protein, membrane lipids, carbohydrate, and DNA, which need subsequent repair[30].

The ability of monocytes to present antigen has been shown to be compromised in acute hyperglycemia[31]. Further there is an increased level of pro-inflammatory cytokines such as TNF-alpha, IL-1beta and IL-6 with hyperglycemia and an increased rate of neutrophil apoptosis in response to LPS challenge[31]. A new paradigm for the human immunological response to severe injury based on the pattern of gene expression by leucocytes after injury postulates that the early leucocyte genomic response is consistent with simultaneously increased expression of genes involved in the systemic inflammatory, innate immune, and compensatory anti-inflammatory responses, and also with the simultaneous suppression of genes involved in adaptive immunity[32].

There is significant endothelial dysfunction associated with even transient hyperglycemia[26]. High glucose levels are also known to impair the microvasculature's ability to relax in the presence of vasodilating stimuli such as nitric oxide, and to promote the adherence and sequestration of neutrophils and monocytes into peripheral tissue[31]. This could be a reason why morbidity and mortality are increased in association with hyperglycemia in diseases directly related to the vascular endothelium, as described later in this review.

EFFECT OF FEEDING

The association between the development of hyperglycemia during total parenteral nutrition (TPN) and poor clinical hospital outcome is well established[33]. Patients with hyperglycemia during TPN have higher incidence of death, infection, and renal failure[34]. Furthermore, the blood glucose values before and within 24 h of initiation of TPN may have special predictive value of mortality and complications, as shown in a study of 276 predominantly critically ill medical and surgical patients[33].

Enterally and parenterally supplied carbohydrates do not have an equal effect on the insulin response or on the resultant blood glucose concentrations[34]. Parenteral feeding bypasses the first-pass control mechanisms of the liver, where splanchnic glucose uptake by first-pass extraction from the portal vein and hepatic artery does not occur. Furthermore, the transit of glucose and fats through the patient's gut liberate glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, among other hormones, that stimulate insulin secretion and decrease gut motility, thereby controlling the rate of nutrient absorption[34,35]. These adaptive mechanisms for regulated clearance of metabolites are absent when nutrients are given parenterally.

In addition to this, the insulin response has been found to be higher when the carbohydrate load is administered parenterally in healthy volunteers[36]. There is no clear explanation for this phenomenon. However, this clearly has an implication on the amount of insulin needed to cover a parenteral glucose load as compared to an enteral load, which may not be attainable by a critically ill patient. Furthermore, the type of fat included in parenteral feeding affects glucose metabolism indirectly with polyunsaturated fatty acids contributing to worse insulin resistance and hyperglycemia compared to monounsaturated fatty

acids[34]. On the other hand, none of the enteral formulations have been shown to be distinctly superior to prevent hyperglycemia in the critically ill (standard *vs* elemental, high fiber or diabetes-specific formulas)[37-43].

In the initial Leuven trial[1], parenteral nutrition supplemented insufficient enteral feeding, whereas in the NICE-SUGAR[7] study, patients were fed enterally exclusively. The administration of insulin during hypocaloric feeding may have increased the risk of hypoglycemia in the NICE-SUGAR[7] study. On the other hand, the administration of insulin in the initial Leuven trial may have counterbalanced the parenteral carbohydrate load.

A meta-analysis of prospective randomized controlled trials (pooled study population of 11425) by Marik *et al*[44] demonstrated a significant relationship between the proportion of calories provided parenterally and the treatment effect of insulin therapy (defined as 28-d mortality in this study).

SPECIAL POPULATIONS

Newly diagnosed hyperglycemia in a study of 2030 patients admitted to a general medical center was associated with a higher rate of ICU admission and with an increased risk for adverse outcome compared with patients who had diabetes and those who were normoglycemic[45]. In fact tight glucose control may be more beneficial in patients without diabetes[46].

A meta-analysis of 35 randomized control trials in surgical ICUs showed that insulin therapy decreased short-term mortality by 15%[47]. Numerous studies have shown a direct relationship between the extent of stress hyperglycemia and mortality in patients in the ICU. In critically ill non-diabetic patients who sustained a myocardial infarction, a meta-analysis of 15 observational studies reported an almost fourfold higher risk of death in patients whose glucose levels ranged from 110-144 mg/dL[48]. Similarly, a meta-analysis of 32 observational studies demonstrated that acute hyperglycemia after stroke was associated with an increased risk for in-hospital mortality and poor functional recovery[49].

A very large retrospective cohort study of over 250000 patients demonstrated that admission diagnosis was a modifier of the effect of admission hyperglycemia on outcome[50]. In other words, specific diagnoses have a greater association between initial hyperglycemia and mortality, including acute myocardial infarction, unstable angina, arrhythmia, pulmonary embolism, sepsis, and intracerebral hemorrhage[50]. This suggests that benefit from tight glucemic control and the glucose control strategies that are most may vary by patient population. IIT may be especially beneficial in the surgical ICU[46,47,51]. Furthermore, the list of diagnoses with the high association between initial hyperglycemia and mortality are those that involve the vascular endothelium, which leads to the hypothesis that tight glucose control may exert its beneficial effect on the endothelium.

Operative patients

The appropriate target glucose level for elective perioperative cases is currently under investigation. A large study of 11633 patients by Kwon *et al*[52] associated perioperative hyperglycemia in elective colorectal and bariatric surgery with increased risk of infection, reoperative intervention, and death[52]. The authors defined hyperglycemia as a serum glucose > 180 mg/dL and best effectiveness of glucose control as being < 130 mg/dL.

We initially evaluated the impact of preoperative hyperglycemia in a series of 252 non-diabetic trauma patients[53]. Elevated serum glucose on admission, defined as glucose greater than 200 mg/dL, was found to be a predictor of postoperative infection, hospital and ICU length of stay, and mortality.

Bláha *et al*[54] conducted a single center randomized controlled trial with 2383 cardiac surgery patients and showed that the initiation of insulin therapy perioperatively reduced postoperative complications (23.2% *vs* 34.1%, 95%CI: 0.60-0.78). This effect was seen most prominently in non-diabetic patients with a risk reduction of 37% (21.3% *vs* 33.7%, RR = 0.63, 95%CI: 0.54-0.74).

The risk of hypoglycemia may be exacerbated in operative patients as the relationships between hypoglycemia and death in the NICE-SUGAR[7] study was stronger among postoperative patients[7]. On the hand, insulin administration itself may have positive implications on the risk of infection, operative intervention, and mortality in cases of hyperglycemia[52].

Trauma

Trauma is clearly is recognized as a distinct population with respect to the injury-induced hyperglycemic stress response and its adverse effect on outcome. These patients are typically previously healthy and the traumatic effect of glucose elevation and variability on outcome seems to be especially pronounced[55].

First, hyperglycemia on admission (serum glucose greater than or equal to 200 mg/dL) is a predictor of morbidity and mortality[56]. Yendamuri *et al*[57] evaluated 738 general trauma patients and found that patients who had hyperglycemia on admission had a significantly greater ICU stay and mortality, as wells as higher infectious morbidity including pneumonia, urinary tract infections, wound infections, and bacteremia. Sung *et al*[58] conducted a prospective study of 1003 patients also comparing glucose levels on admission in trauma patients and found a 2.2 fold greater risk of mortality in patients who had hyperglycemia on admission than patients who are normoglycemic on admission and a significantly higher overall infection rate (52% *vs* 32%). The effect persisted after adjustment for age and injury severity.

Second, glucose control was found to be most beneficial in the first week of hospitalization in trauma patients. This time course fits the clinical course of

trauma patients, as the highest peak of infection is at the end of the first week of hospitalization and a peak of deaths occurs in the second week as a result of sepsis and organ dysfunction. Glucose control in the first week significantly influences these events. Bochicchio *et al*[59] evaluated 942 critically ill trauma patients' glucose levels and glucose patterns prospectively. Glucose levels were categorized as all low, all moderate, all high, improving, worsening, and highly variable. When controlling for age, ISS and gender, high, worsening and highly variable hyperglycemic patterns were highly predictive of increased ventilator days, ICU and hospital days, infection, and mortality. The changes in blood glucose over time, namely glucose variability, has thus been shown to be associated with outcome in trauma patients. In another study over 28 d, Bochicchio *et al*[56] studied 894 patients and found a 17-fold increase in odds of death in patients with high glucose levels over the first week and a 1.5 fold increase in infection. This effect persisted regardless of subsequent glucose control. To further elucidate this, Bochicchio *et al*[60] evaluated both degree of glucose elevation and variability post trauma. By combining both of these variables and creating an acute glucose elevation score (AGE score) *via* a computational algorithmic model, an AGE score of 4 was found to have a 91% positive predictive value for diagnosis of infection[60].

Third, glucose control in trauma patients is associated with improved outcomes. In a large prospective quasi-experimental time series of 2120 patients[61], patients assigned to the experimental group (glucose target 100-150 mg/dL) had fewer infections and greater survival. The benefit from glucose control in trauma patients is expected to be greatest when glycemic control is initiated early.

HYPOGLYCEMIA

The benefits of tight glucose control are counterbalanced by the harm of hypoglycemia. In the first Leuven study[1] where intensive glucose therapy was shown superior, the rate of hypoglycemia in the treatment group was 5.1% compared to 0.8% in the control group. In the NICE-SUGAR[7] trial, the rate was 6.8% compared to 0.5%. Patients with moderate hypoglycemia in the latter study (41 to 70 mg/dL) have a 40% increased risk of death compared to patients without hypoglycemia, while patients with severe hypoglycemia had twice the risk of death than the control group. Note that the conventional glucose targets in these two studies[1,7] are different, meaning that the maximum size of the benefit from controlling glucose is likely different in the two studies.

The trade-off between the benefit of preventing hyperglycemia and the harm of hypoglycemia is elegantly exemplified by a sensitivity analysis conducted on a large retrospective cohort of critically ill patients by case-matching sentinel cases of hypoglycemia against cases with no hypoglycemia at a ratio of 1:3[62]. The result was that in this cohort, the benefit of tight glucose control would have been eliminated if the rate of hypoglycemia was four times higher and the mortality attributed to severe hypoglycemia was twice as high. This question of risk-*vs*-benefit comes into sharp focus with the closure of two large intensive glucose management trials, the German VISEP[9] and European GLUCONTROL[8]. Importantly, the mortality rate in the latter study was significantly increased in patients with similar severity scores who experienced hypoglycemia[8].

Thus one must ask, what is the appropriate target of glucose that optimizes the benefit of reducing hyperglycemia at an acceptable rate of hypoglycemia? The answer, in the opinion of the authors is dependent on multiple factors. First, not all glucose measurement meters are created equal. Many widely used methods are fraught with inaccuracies and are especially problematic in the critically ill population[63,64]. Protocols and the adherence to them also affect the rate of hypoglycemia. Different institutions have different abilities to implement complex protocols. Disease processes are likely different in the glucose patterns that they generate and in the degree and timing of glucose control that is most beneficial. Having said this, the authors believe that continuous or near continuous glucose monitoring would provide a much needed solution to glucose control. The true answer is normal glucose range (80-110 mg/dL) if performed safely without hypoglycemia.

GLUCOSE VARIABILITY

In addition to hyper and hypoglycemia, variability in the glucose measurements of a particular patient seem to have a bearing on outcome. Several studies have addressed this issue. In a cohort of 7049 critically ill patients, the coefficient of variability calculated from the standard deviation of glucose measurements for each patient showed increased mortality risk with greater variation[65]. Interestingly, in patients who had diabetes, the variability of glucose measurements had a higher correlation with ICU mortality than the absolute value of blood glucose[65].

More time spent in range (glucose level within protocol) is a strong predictor of outcome. In a study of 784 patients admitted to ICU, it was found that the more time spent in the 72-126 mg/dL range, the better the outcome, with 50% of the time in each day being the minimal acceptable threshold based on outcome[66]. A post-hoc analysis of the GLUCONTROL[8] showed similar findings with patients spending more than 50% of the time in the glucose range of 70-126 mg/dL having better outcome[67]. Glucose variability, however, was not addressed in the initial large randomized trials.

In a large study involving 20375 patients of a prospectively collected multicenter dataset, metrics of glycemic variability were measured[68]. In the medical patients, outcome was associated with standard deviation of glucose measurement and the mean of the differences in glucose levels that were more aberrant than the standard deviations[68]. In the surgical patients, the

Table 1 Summary of recommendations for glycemic management

Recommendations	Ref.
In operative patients including trauma, cardiac, and elective surgical patients, it is advised to start a fast acting insulin regimen in the emergency room and perioperatively whenever applicable	[11,32,55]
In trauma patients, glucose control with a target of 100-150 md/dL is reasonable and most important through the first week of hospitalization	[57,61,62]
In elective surgical patients, glucose control with a target of less than 130 mg/dL is advised perioperatively	[32,53]
In patient who will receive parenteral nutrition, intensive insulin therapy is recommended in anticipation of feeding and especially within the first 24 h of initiation	[34,37,42,45]
In patients receiving hypocaloric feeding or with interruption of enteral feeding, less strict glucose control is recommended	[1,11,45]
The rate of hypoglycemia should be a widely adopted quality control parameter. Elevated rates of hypoglycemia should prompt corrective action and changes in policy as needed	[1,8,9,63]
It is important to avoid excursions in glucose levels by titrating insulin treatment conscientiously, especially in diabetic patients, in trauma, and in surgical patients	[61,66,68,69]
Frequent glucose monitoring is advised. To prevent increasing clinician workload, continuous glucose monitoring may be indicated	[64,65,71,72]
Unexplained rises or falls in glucose levels may be a sign of worsening clinical status or infection	[56,60]

latter variables were also significant. In addition to this, a measure of the mean of the differences in glucose levels adjusted for the time between measurements was significant[68]. This indicates that the amount of glucose variability over time may be more important in surgical patients than in medical patients within the surgical population. Bochicchio *et al*[59] reported in a study of 942 critically ill trauma patients, that highly variable glucose patterns were highly predictive of increased ventilator days, ICU and hospital days, infection, and mortality[59].

INSULIN DOSING

It is difficult to make specific recommendations regarding insulin protocols and administration because these depend heavily on the resources of the care facility, the nursing workload, and importantly, the accuracy of the glucose measurement techniques used as point of care. In addition, patients may vary widely in their requirements for insulin dosing and the optimal strategy of glucose control.

The authors believe that there is an under appreciation of the contribution of the primary diagnosis to the requirements of glucose control. For example, in a randomized controlled trial of 2383 cardiac surgery patients[54], starting an insulin protocol as of time of surgery whenever blood glucose reached greater than 110 mg/dL reduced postoperative complications compared to starting an insulin protocol after the patients have greater than 180 mg/dL or are admitted to ICU. In an analysis of prospectively collected data in elective bariatric and colorectal patients, hyperglycemia was associated with increased infectious morbidity and this effect was absent in hyperglycemic patients in the non-extreme range who received insulin on the day of surgery[52,69]. Surgical patients appear to benefit from the initiation of an insulin protocol early in the perioperative period. In trauma patients, early glucose control is important and reduces morbidity and mortality and patients would likely benefit from an insulin protocol started immediately in the emergency department.

One of the major differences between the Leuven study and the NICE-SUGAR trial is the use of parenteral nutrition to supplement insufficient enteral feeding in the Leuven study but the strict adherence to the latter in the NICE-SUGAR[1,7,8] study. Since parenteral feeding causes a greater rise in blood glucose and requires more insulin than an equivalent enteral load[36], it is reasonable that the treatment effect of insulin is increased in these patients. Therefore, patients deserve individual assessment of predicted insulin requirements prior to initiation of feeding and more liberal dosing in anticipation of increased needs.

It is unlikely that one size fits all for insulin protocols. We recommend that hospitals and individual departments develop glucose protocols per patient population and taking into account the patient's diagnosis and plan of therapy, premorbid glucose status, and nutritional support, as well as the personnel resources and best accuracy of glucose measurements available. The target of glucose therapy and starting insulin doses and rate of change should be updated with the existing evidence for each patient population as well as the feedback of hypoglycemia rates in each hospital service. Recommendations for glucose management in critically ill populations are summarized in Table 1.

Advances in glucose monitoring technology including near continuous glucose monitors and neural prediction networks[70-72] are under development to improve glucose measurement accuracy, decrease staff workload, and self-adjust for changing insulin needs by real-time prediction of glucose levels.

CONCLUSION

Glucose control is of therapeutic importance in critically ill patients. Hyperglycemia is the result of the metabolic response to stress and is modulated by the treatment of the critically ill, including exogenous glucose sources and nutrition. Glucose levels in critically ill patients have both prognostic and therapeutic value. Glucose control is best applied by consistent control of glucose in a therapeutic range without incurring hypoglycemia or variability. Patients with different diagnoses may have different needs for glucose management. The advent of more precise glucose monitors and automated systems would help improve the degree of glucose control possible without the harmful effects of hypoglycemia and therefore improve outcome.

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