厚生労働科学研究費補助金
がん臨床研究事業

非治癒因子を有する進行胃癌に対する胃原発巣切除の意義に関する国際共同研究

平成23～25年度　総合研究報告書

研究代表者　　辻仲 利政

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厚生労働省科学研究費補助金（がん臨床研究事業）
Ⅰ総括研究報告書

非治癒因子を有する進行胃癌に対する胃原発巣切除の意義に関する国際共同研究

研究代表者　辻仲利政
市立貝塚病院　　院長

研究要旨

治癒切除不能胃癌を対象とした多施設共同ランダム化比較第Ⅲ相試験を行い、減量手術の意義を検証する。肝転移（H1）、腹膜播種（P1）、#16a1/b2 大動脈周囲リンパ節転移（M1）の非治癒因子のうち１つのみを有する場合を本試験対象とし、JCOG 初の日韓国際共同試験として実施された。予定登録症例は 330 名、症例登録期間は 4 年、追跡期間 2 年。総研究期間：6 年であった。予定登録数の半数が登録された時点で中間解析を予定した。中間解析の結果、化学療法群に対する減量手術群の優越性が認められず試験中止が勧告された。中止勧告に従い試験中止を決定した。試験中止までに 175 例の症例登録が得られた。本研究結果より標準治療が化学療法単独であることが確認された。

研究分担者
栗田　啓　　国立病院機構四国がんセンター、上部消化管外科、副院長
木下　敬弘　独立行政法人　国立がん研究センター東病院、胃外科科長
寺島　雅典　静岡県立静岡がんセンター胃外科　消化器外科部長
木村　豊　　市立堺病院　胃食道外科担当部長
津田　政広　兵庫県立がんセンター　消化器内科　部長
畑　　啓昭　独立行政法人国立病院機構　京都医療センター
梨本　篤　　新潟県立がんセンター新潟病院　副院長
田村　茂行　関西労災病院　副院長
今本　治彦　近畿大学医学部付属病院　外科　教授
山上　裕樹　和歌山県立医科大学第２外科　教授

A. 研究目的

治癒切除不能な進行胃癌に対して、減量的胃切除術が選択される理由は、胃原発巣は化学療法が比較的奏効しにくいこと、胃切除により原発巣に起因する狭窄や出血などを回避できることである。しかし、減量手術を行うことにより、各種の術後合併症が発生する、術後化学療法の開始が遅れる、化学療法の完遂率が低下する、などの不利益がある。減量的胃切除により生存期間の延長が得られたとする報告が多いが、化学療法を行うか、胃切除を行うかの対象選択バイアスが大きい。減量手術の意義は、最も科学的に信頼できるランダム化比較第Ⅲ相試験により検証する必要がある。

本研究は、減量的胃切除の意義を検証する世界で始めてのランダム化比較第Ⅲ相試験であり、JCOG 初の日韓国際共同試験として行われる。世界の胃癌の約 60%は東アジアで発生しており、日本と韓国はともに世界の胃癌治療の先導する役割を担っている。

B. 研究方法

JCOGプロトコール（JCOG0705）に記載された方法に従って研究は行われる。

組織学的に胃癌と証明され、あらかじめ定められた適格規準をすべて満たす患者を登録適格患者とする。

登録・割付に関して、日本の施設は登録適格性確認票を JCOG データセンターに電話連絡または FAX 送信にて、韓国の施設は国立ソウル大学病院データセンターに Web 送信にて、登録を行う。登録にあたって治療群は日韓それぞれのデータセンターでランダムに割りつける。ランダム割り付けに際しては、国（日本/韓国）を層別因子とし、施設、リンパ節転移(N0-1/N2-3)、非治癒因子（H1/P1/ M1）を調整因子とする最小化法を用いる。

治療計画として、化学療法単独群（A 群）では登録後 14 日以内に S-1+CDDP による化学療法、減量手術群（B 群）では登録後 21 日以内に減量手術を行い、その後 S-1+CDDP による術後化学療法を開始する。両群における化学療法は、中止規準に該当しない限り継続する。B 群で行う減量手術は、開腹による胃切除および D1 郭清を原則とし、完全な D2 郭清や他臓器の合併切除は許容しない。

本試験の主要評価項目は生存期間、副次評価項目は無増悪生存期間および有害事象発生割合とした。本試験の A 群における 2 年生存割合は 20～25%程度と予想し、B 群においては A 群に対して 2 年生存割合で 10%の上乗せ効果を期待し、α=0.05(片側)、検出力 80%、登録期間 4 年、追跡期間 2 年とし、必要症例数は両群合計 330 名とした。半数の 165 例が登録された時点で、第 1

回目の中間解析を行うが、症例登録は継続する。試験中止の条件は、あらかじめプロトコールに規定した。

（倫理面での配慮）

本試験では、試験の参加に際しては同意説明文を用いた説明と文書での同意を前提とし、研究参加に関して各施設の倫理審査委員会の承認を受ける。研究は、JCOG 効果安全評価基準に基づいて行わる。データの取り扱いに際しては、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。倫理面での配慮は十分保障されている。急送報告を必要とする有害事象に関しては、リエゾン事務局を通じて両国での情報交換を行う。

C. 研究成果

平成 19 年 12 月に JCOG プロトコール審査委員会での承認が得られ、平成 20 年 1 月に日本においてキックオフ会議を行い、その後各施設の IRB の承認を得て試験を開始した。。両国から定期モニタリングレポートが提出され、相互検討を行い、研究の同質性を担保している。平成 25 年 1 月末までに 13 回の日韓研究者会議を開催した。同時に、韓国側のデータセンター（ソウル大学）と JCOG データセンターとの相互交流と意見交換を行ってきた。

平成 24 年度において当初の登録予定期間が終了するため、平成 25 年 8 月までは、現在のプロトコールを改定しないこと、出来るだけ速やかに中間解析に至ること、中間解析で試験継続が決定されたときには症例数の見直しを行うことを合意した。平成 25 年 5 月までに 164 例の登録が得られ、中間解析を平成 25 年 9 月 14 日に行った。平成 23 年末からシンガポール（国立シンガポール大学胃外科）が新たに研究に参加し、平成 25 年 6 月に症例登録が得られた。現在 3 カ国の国際共同研究となっている。中間解析の結果、全体として減量手術群の予後が化学療法群のものより下回っており、試験中止基準に該当するため、効果安全性評価委員会から試験中止が勧告された。日韓の研究責任者はこの勧告を受け入れ試験中止を決定した。減量手術の治療効果には、日韓の差が認められた。すなわち、日本では減量手術群の予後は明らかに劣っていたが、韓国では化学療法群の予後を下回ることはなかった。サブセット解析の結果、韓国では下部胃癌の登録が多く、その下部胃癌において減量手術群の優越性が認められた。上部胃癌では減量手術群は有意に劣っており、日本では上部胃癌の登録が多かった。

D. 考察

中間解析の結果、減量手術群の優越性

が示されなかった。これまで十分なエビデンスがないまま広く行われていた治癒切除不能進行胃癌に対する減量的胃切除術が無効であることが立証された。標準治療は、化学療法単独治療であることが確認された。しかしながら、下部胃癌に対する減量的胃切除が有効である可能性があり、治療オプションの一つとなる。

本研究を日韓国際共同研究として（最終的には３カ国共同研究）行えたため、迅速な症例登録が得られた。日本のみでの症例登録では研究完遂が不可能であったと想定される。プロトコール順守、急送報告および予後追跡の点において、韓国に不備が多く認められた。医師主導臨床試験に不慣れである背景を考慮しても、改善の余地が多い。減量手術の効果において日韓での差が認められたが、その原因が下部胃癌における減量手術の有効性と日韓の部位別登録数の異なりに基づくことが判明した。個々の国で別々に研究を行っていた場合、同じ対象に対して異なる結論が得られていた可能性が高かった。国際共同研究としておこなうことにより、より真実の結果が得られ、結果の共有が可能となった。今回得られた結果の国際的インパクトは非常に大きい。

本研究により、国際共同研究の経験と実績を積むことが出来た。定期交流を重ねることにより、相互の医療環境および保険制度の相違が理解され、研究推進への共同意識を保ち、研究の質を確保する必要性が認識されるようになった。リエゾン事務局を介した相互情報交換が十分機能したとは結論できないが、経験が蓄積されてきた。

本研究の経験を活用して、胃がんに対する新たな治療開発が国際共同研究として行われることが期待される。

E. 結論

非治癒因子を一つ有する治癒切除不能進行胃癌に対しては化学療法が標準治療である。下部胃癌に対する減量手術は治療オプションの一つとなり得る。この結果により、国際共同研究として最良の成果が得られた。

F. 健康危険情報

両国において、健康危険事象が発生した場合の対応システムを確立した。現在までに、日本において治療に関連した重篤な健康危険事象が２例発生した。急送報告を JCOG 効果安全性評価委員会に提出し、回答を得た。回答を日本の研究者には班会議にて周知し、韓国研究者にはリエゾン事務局を通じて報告した。韓国から３例の早期死亡報告があり、JCOG 効果安全性評価委員会にて内２例が治療関連死の可能性ありと判定された。しかしながら、これらの事例に対する韓国側の効果安全性評価がなされておらず、改善を要

求した。

G.研究結果

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H. 知的財産の出願・登録状況

なし

別紙４

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Subcuticular sutures versus staples for skin closure after open gastrointestinal surgery: a phase 3, multicentre, open-label, randomised controlled trial

Toshimasa Tsujinaka, Kazuyoshi Yamamoto, Junya Fujita, Shunji Endo, Junji Kawada, Shin Nakahira, Toshio Shimokawa, Shogo Kobayashi, Makoto Yamasaki, Yusuke Akamaru, Atsushi Miyamoto, Tsunekazu Mizushima, Junzo Shimizu, Koji Umeshita, Toshinori Ito, Yuichiro Doki, Masaki Mori, for the Clinical Study Group of Osaka University on Section of Risk Management

Summary

Background Staples have been widely used for skin closure after open gastrointestinal surgery. The potential advantages of subcuticular sutures compared with staples have not been assessed. We assessed the differences in the frequency of wound complications, including superficial incisional surgical site infection and hypertrophic scar formation, depending on whether subcuticular sutures or staples are used.

Methods We did a multicentre, open-label, randomised controlled trial at 24 institutions between June 1, 2009, and Feb 28, 2012. Eligible patients aged 20 years or older, with adequate organ function and undergoing elective open upper or lower gastrointestinal surgery, were randomly assigned preoperatively to either staples or subcuticular sutures for skin closure. Randomisation was done via a computer-generated permuted-block sequence, and was stratified by institution, sex, and type of surgery (ie, upper or lower gastrointestinal surgery). Our primary endpoint was the incidence of wound complications within 30 days of surgery. Analysis was done by intention to treat. This study is registered with UMIN-CTR, UMIN000002480.

Findings 1080 patients were enrolled and randomly assigned in a one to one ratio: 562 to subcuticular sutures and 518 to staples. 1072 were eligible for the primary endpoint and 1058 for the secondary endpoint. Of the 558 patients who received subcuticular sutures, 382 underwent upper gastrointestinal surgery and 176 underwent lower gastrointestinal surgery. Wound complications occurred in 47 of 558 patients (8·4%, 95% CI 6·3–11·0). Of the 514 who received staples, 413 underwent upper gastrointestinal surgery and 101 underwent lower gastrointestinal surgery. Wound complications occurred in 59 of 514 (11·5%, 95% CI 8·9–14·6). Overall, the rate of wound complications did not differ significantly between the subcuticular sutures and staples groups (odds ratio 0·709, 95% CI 0·474–1·062; p=0·12).

Interpretation The efficacy of subcuticular sutures was not validated as an improvement over a standard procedure for skin closure to reduce the incidence of wound complications after open gastrointestinal surgery.

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Department of Surgery, Kaizuka City Hospital, Osaka, Japan (T Tsujinaka MD); **Department of Surgery, National Hospital Organisation Osaka National Hospital, Osaka, Japan** (K Yamamoto MD, A Miyamoto MD); **Department of Surgery, NTT West Osaka Hospital, Osaka, Japan** (J Fujita MD); **Department of Surgery, Higashiosaka City General Hospital, Osaka, Japan** (S Endo MD); **Department of Surgery, Osaka General Medical Centre, Osaka, Japan** (J Kawada MD); **Department of Surgery, Kansai Rosai Hospital, Hyogo, Japan** (S Nakahira MD); **Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan** (T Shimokawa PhD); **Department of Gastroenterological Surgery** (S Kobayashi MD, M Yamasaki MD, T Mizushima MD, Prof K Umeshita MD, Prof T Ito MD, Prof Y Doki MD, Prof M Mori MD), **and Department of Complementary and Alternative Medicine** (Prof T Ito), **Graduate School of Medicine, Osaka University, Osaka, Japan; Department of Surgery, Osaka-Koseinenkin-Hospital, Osaka, Japan** (Y Akamaru MD); **and Department of Surgery, Osaka Rosai Hospital, Osaka, Japan** (J Shimizu MD)

Correspondence to:
Dr Toshimasa Tsujinaka, Department of Surgery, Kaizuka City Hospital, 3-10-20 Hori, Kaizuka, 597-0015 Osaka, Japan
tsujinaka@hosp.kaizuka.osaka.jp

Introduction

Wound complications are among the most common issues reported after surgery, and are often very problematic for patients in terms of cosmetic appearance, decreased quality of life, prolonged hospital stays, and increased health-care costs.[1,2] Several publications have addressed ways to reduce the risk of wound complications associated with surgery,[3–6] such as intraoperative administration of antimicrobial prophylaxis,[4,5] skin preparation, barrier retractional wound protection,[7] use of absorbable sutures during intraperitoneal procedures,[8,9] and pulsatile lavage irrigation of wounds before closure.[10,11] Triclosan-coated sutures significantly reduced the rate of surgical site infections compared with conventional uncoated sutures in various types of surgery.[12]

Because of the increase in the number of patients with preoperative comorbidities that are risk factors for wound complications, such as malnutrition,[13] diabetes mellitus,[14] and obesity,[15] new, innovative approaches will be necessary to decrease the risk of wound complications after surgery. Subcuticular suturing for skin closure is an attractive alternative for skin approximation in most types of surgery. It is often used in plastic surgery because of the low incidence of wound complications and good cosmetic appearance.[16–18] Compared with staples, several clinical trials have shown that subcuticular sutures are associated with a significantly lower incidence of wound complications and better cosmetic results after orthopaedic surgery,[19] cardiovascular surgery,[20,21] and caesarean section.[22,23]

In 242 patients undergoing coronary artery bypass graft surgery, Johnson and colleagues[24] prospectively closed half of each sternal and saphenous vein harvest wound with staples and half with intradermal sutures. The incidence of wound infection was similar with both methods, but significantly fewer wound complications were noted with subcuticular sutures than with staples. Additionally, patients who expressed a preference preferred sutures to staples. Basha and investigators[25] randomly assigned 435 patients undergoing caesarean delivery to stainless steel staples or subcuticular 4-0 monocryl sutures. They

reported that staple closure was associated with a four-times increased risk of wound separation (adjusted odds ratio [OR] 4·66, 95% CI 2·07–10·52; p<0·001) and poor patient satisfaction.

These trials had been done for class 1 surgical procedures—ie, clean surgery. However, the benefit of subcuticular sutures in gastrointestinal surgery, a class 2 (clean-contaminated) surgery that is associated with a high incidence of wound complications,[15,26,27] has not been fully examined.[28] Staples are the most commonly used technique for skin closure during gastrointestinal surgery because of convenience and speed. Because no consensus has been reached about how to apply findings from class 1 surgery to class 2 surgery, an optimum method of skin for gastrointestinal surgery remains to be established.

We investigated differences in prevention of wound complications between subcuticular sutures and staples after elective upper and lower gastrointestinal open surgery.

Methods

Study design and participants

We did a large-scale, multicentre, open-label, phase 3 randomised controlled trial at 24 institutions in Japan from June 1, 2009, to Feb 28, 2012. The study was organised by the Clinical Study Group of Osaka University on Risk Management (OSGO-RM), which is composed of hospitals affiliated from the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University.

Eligible patients were undergoing elective upper or lower gastrointestinal surgery, aged 20 years or older, and had adequate organ function. Patients undergoing abdominoperineal resection for rectal cancer were also eligible, but we only assessed abdominal wounds for outcomes. We excluded patients needing emergency or laparoscopic surgery, with a history of laparotomy with a midline incision, or with long-term corticosteroid use; active infection such as peritonitis, pneumonia, or urinary tract infection; massive ascites; coagulopathy or other disorders that would preclude study participation; uncontrolled or insulin-treated diabetes; mental illness, poor general condition; severe cardiopulmonary disease; or who were deemed by surgeons to be inappropriate for participation in a randomised trial. The institutional review board of each hospital approved the protocol. All patients provided written informed consent before randomisation. We did not collect data on the number of patients approached and assessed for eligibility.

Randomisation and masking

Patients were recruited by the investigators and treatment allocation was made preoperatively after confirming eligibity.

Enrolment was done through a web-based system established for this trial and randomisation by a computer-generated permuted-block sequence. The size of the blocks used for randomisation was four. Patients were randomly assigned (1:1) to either subcuticular sutures or staples for skin closure and balanced according to institution, sex, and type of surgery (ie, upper or lower gastrointestinal open surgery). Investigator surgeons were informed of the treatment allocation via the internet and did the procedures. Patients and investigators were not masked to group assignment. The data centre, based at the Multicenter Clinical Study Group at Osaka University was responsible for treatment allocation, central monitoring, and statistical analyses under the supervision of the statistician in charge.

Procedures

In the subcuticular suture group, surgeons used interrupted subcuticular sutures with 3-0 or 4-0 monofilament absorbable suture (polydioxanone; PDS-II Ethicon, Tokyo, Japan). The interval of the sucuticular sutures was 15–25 mm and the length of the bite of sutures was 15–25 mm from the edge of the skin. Under this condition, the skin could be closed tightly. Use of sterile strips or skin glue for epidermal approximation in addition to subcuticular sutures was an institutional choice. In the staples group, metallic skin staples, which were the choice of individual institutions, 10–15 mm apart were used. Approximation of the fat layer was not allowed in the either group. Before the trial, investigators from participating institutions were instructed on how to do subcuticular sutures during the trial. A video in which a plastic surgeon used the subcuticular suturing technique (adopted as the standard) was provided to each participating institution. The standard procedure was also demonstrated at each investigator meeting. Investigators and physicians in training met yearly to examine how subcuticular sutures were done.

All participating institutions were asked to follow the guidelines about prevention of surgical site infections issued by the US Centers for Disease Control and Prevention (CDC).[29] Surgical gloves and instruments were changed before wound closure. Absorbable monofilament sutures were used for approximation of the fascia, and the subcutaneous space was irrigated with saline without added antibiotics. Intra-abdominal drain placement through a separate incision away from the operative incision was permitted but drainage of the wound was not allowed. Skin preparation techniques, prophylactic antibiotic administration, the volume of saline used for intra-abdominal irrigation, dressing methods, and timing of postoperative staple removal, perioperative care, and wound management were according to each participating institution's respective standards.

Our primary outcome was incidence of wound complications within 30 days of surgery. The secondary outcome was the incidence of hypertrophic scar formation 6 months after surgery. Wound complications were defined as the presence of at least one of several signs or symptoms necessitating treatment: wound disruption,

stitch abscess, abscess caused by metal allergy, seroma or haematoma, or superficial incisional surgical site infections. Superficial incisional surgical site infections are defined by the CDC[29] as infections occurring within 30 days of surgery that implicate only the skin or subcutaneous tissue of the incision. Diagnosis of superficial incisional surgical site infection must satisfy one or more of several criteria: purulent drainage (with or without laboratory confirmation) from the superficial incision, organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, or at least one of the signs or symptoms of infection (pain or tenderness, localised swelling, redness or heat, and superficial incision deliberately opened by the surgeon, unless the incision is culture-negative). Infection control personnel monitored and detected surgical site infections during patients' hospital stays. Changes noted in the wound were not defined as wound complications if they did not necessitate treatment. When superficial incisional surgical site infections and other wound complications coexisted in the same patient, we defined the complication as superficial incisional surgical site infections. We defined hypertrophic scar as a widened or elevated unsightly scar with erythema or pigmentation.

Responsible surgeons checked for the presence or absence of wound complications every day during the hospital stay and at every outpatient visit until 30 days after surgery. They were also responsible for checking for the presence or absence of hypertrophic scar formation at 6 months after surgery, and measured the width and length of detected hypertrophic scars. Before starting the trial, the principal investigator showed typical cases of various wound complications and hypertrophic scars, and consensus about all types of wound complications was reached by the investigators.

Statistical analysis

We planned a sample size of 530 patients per treatment group when we designed the trial. Such a sample size would provide power of 80% with a two-sided significance level of 0·05 to detect superiority in the reduction of the frequency of wound complications. Wound complications were anticipated in 11% of patients in the staples group and 6% in the subcuticular sutures group, allowing for a loss to follow-up of roughly 10%. The projected accrual period was 2 years and no interim analyses were planned.

We did the analysis on a modified intention-to-treat basis. We expressed continuous numerical data as medians and IQRs or means and SDs, when appropriate, and distribution of dichotomous data in percentages with 95% CIs. We used Fisher's exact test to compare binary variables and the Mann-Whitney *U* test to compare continuous variables. All p values of less than 0·05 were deemed significant.

The primary outcome was analysed with Fisher's exact test, and we used the Mantel-Haenszel test to adjust for the type of surgery, a potential confounding factor, which was not prespecified in the protocol. We used Fisher's exact test to analyse the secondary outcome and to calculate and compare outcomes as a post-hoc analysis on the basis of type of surgery.

We analysed thickness of subcutaneous fat (objectively classified by the surgeon as either thin, normal, or thick), American Society of Anesthesiologists (ASA) physical status classification,[30] operative time, intraoperative blood loss volume, duration of prophylactic antibiotics, presence of drainage tube and duration of drainage, and use of postoperative anticoagulant therapy as variables. Subgroups were analysed with logistic regression to assess for statistical interactions between treatments in various subgroups. Because of the exploratory nature of subgroup comparisons, we report test results without multiplicity adjustments for type I error. This study is registered with UMIN-CTR, UMIN000002480. UMIN-CTR is one of the network members of the Japan Primary Registries Network, which meets WHO registry criteria.

Role of the funding source

The sponsor had no roles in the study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had full access to all

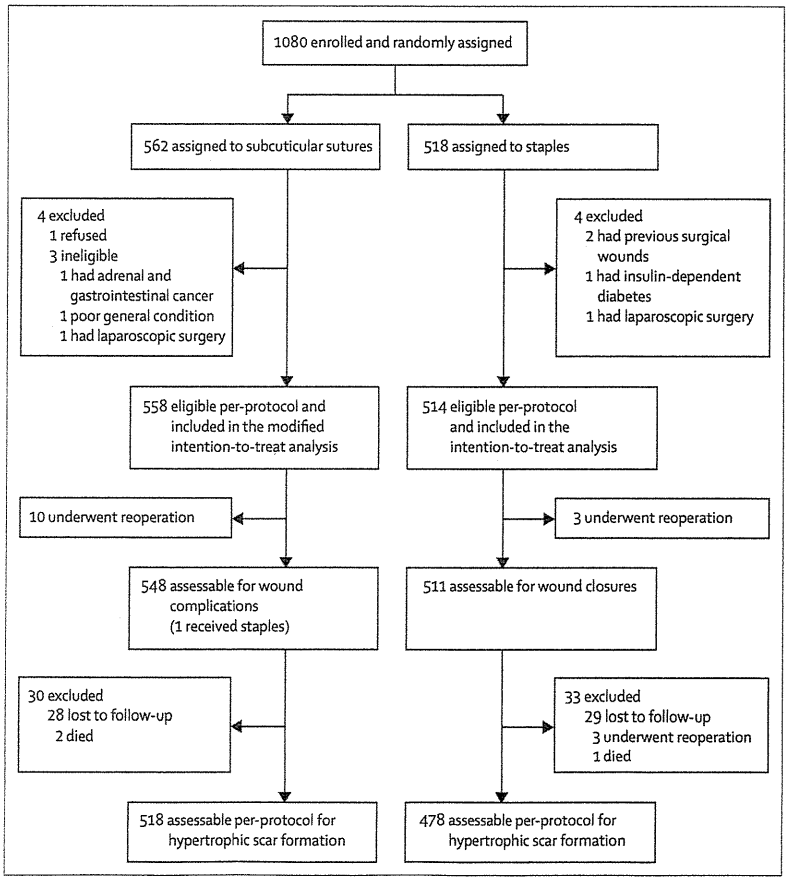

Figure 1: **Trial profile**

	Subcuticular sutures (n=562)	Staples (n=518)
Age (years)	68 (61–75)	68 (61–74)
Sex		
Male	388 (69·0%)	365 (70·5%)
Female	174 (31·0%)	153 (29·5%)
Surgery		
Upper gastrointestinal	385 (68·5%)	417 (80·5%)
Lower gastrointestinal	177 (31·5%)	101 (19·5%)
Thickness of subcutaneous fat*		
Thick	143 (25·6%)	109 (21·2%)
Standard	328 (58·8%)	317 (61·6%)
Thin	87 (15·6%)	89 (17·3%)
ASA physical status classification*		
1	201 (36·0%)	201 (39·0%)
2	313 (56·1%)	273 (53·0%)
3	44 (7·9%)	41 (8·0%)
Operative time (min)*	228 (180–270)	218 (175–264)
Blood loss (mL)	230 (100–430)	244 (120–450)
Wound protection†		
Surgical drape	535 (95·9%)	497 (96·3%)
Gauze	10 (1·8%)	6 (1·2%)
None	13 (2·3%)	13 (2·5%)
Duration of antibiotic prophylaxis (days)*		
1	379 (67·9%)	373 (72·4%)
2	33 (5·9%)	22 (4·3%)
3	100 (17·9%)	86 (16·7%)
≥4	46 (8·2%)	34 (6·6%)
Duration of drain insertion (days)*		
0 (ie, no drain)	118 (21·1%)	108 (21·0%)
1–3	50 (9·0%)	34 (6·6%)
≥4	390 (69·9%)	373 (72·4%)
Duration of hospital stay after surgery (days)	14 (11–21)	15 (12–21)
Anticoagulation therapy‡		
Yes	130 (23·3%)	96 (18·6%)
No	429 (76·7%)	420 (81·4%)

Data are n (%) or median (IQR). ASA=American Society of Anesthesiologists.[20] *Data missing for four patients in the subcuticular sutures group and three patients in the staples group. †Data missing for four patients in the subcuticular sutures group and two patients in the staples group. ‡Data missing for three patients in the subcuticular sutures group and two patients in the staples group.

Table 1: **Baseline demographic and clinical characteristics**

	Subcuticular sutures (n=385)	Staples (n=417)
Diseases		
Gastric cancer	375 (97·4%)	403 (96·6%)
Gastric submucosal tumour	6 (1·6%)	9 (2·2%)
Other	4 (1·0%)	5 (1·2%)
Procedures		
Total gastrectomy	149 (38·7%)	143 (34·3%)
Distal gastrectomy	186 (48·3%)	219 (52·5%)
Proximal gastrectomy	19 (4·9%)	16 (3·8%)
Exploratory laparotomy	4 (1·0%)	4 (1·0%)
Other	27 (7·0%)	35 (8·4%)

Data are n (%).

Table 2: **Types of diseases and surgical procedures in patients undergoing upper gastrointestinal surgery**

	Subcuticular sutures (n=177)	Staples (n=101)
Diseases		
Colon cancer	98 (55·4%)	51 (50·5%)
Rectal cancer	71 (40·1%)	48 (47·5%)
Anal cancer	2 (1·1%)	1 (1·0%)
Other	6 (3·4%)	1 (1·0%)
Procedures		
Right hemicolectomy	41 (23·2%)	28 (27·7%)
Left hemicolectomy	44 (24·9%)	8 (7·9%)
Low anterior resection	61 (34·5%)	38 (37·6%)
Abdominoperineal resection	11 (6·2%)	10 (9·9%)
Partial resection of colon	9 (5·1%)	10 (9·9%)
Other	11 (6·2%)	7 (6·9%)

Data are n (%).

Table 3: **Types of diseases and surgical procedures in patients undergoing lower gastrointestinal surgery**

the data and was responsible for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1080 patients from 24 institutions were enrolled and randomly assigned—562 to subcuticular sutures and 518 to staples. Assessment of case report forms showed that four patients in each group were ineligible for inclusion, and thus the modified intention-to-treat population comprised 558 patients in the subcuticular sutures group and 514 in the staples group (figure 1). Ten patients in the subcuticular sutures group and three in the staples group needed reoperation within 30 days, which met the exclusion criterion, a history of laparotomy, and thus were not assessed for wound complications.

Distribution of most demographic and clinical characteristics of enrolled patients was balanced between groups except type of surgery (table 1). Tables 2 and 3 show details of the diseases and surgical procedures in the two groups. 417 patients who underwent upper gastrointestinal surgery were allocated to the staples group and 385 to the subcuticular sutures group, and 177 patients who underwent lower gastrointestinal surgery were allocated to the subcuticular sutures group and 101 to the staples group.

In the subcuticular sutures group, wound complications occurred in 47 of 558 (8·4%, 95% CI 6·3–11·0) patients, including 36 (6·4%, 4·6–8·8) patients with superficial incisional surgical site infections. In the staples group, wound complications occurred in 59 of 514 patients

	All patients				Upper gastrointestinal surgery				Lower gastrointestinal surgery			
	Subcuticular suture (n=558)	Staples (n=514)	Odds ratio (95% CI)	p	Subcuticular sutures (n=382)	Staples (n=413)	Odds ratio (95% CI)	p	Subcuticular sutures (n=176)	Staples (n=101)	Odds ratio (95% CI)	p
Primary outcome												
Wound complication rate*	47 (8·4%)	59 (11·5%)	0·709 (0·474–1·062)	0·12	29 (7·6%)	39 (9·4%)	0·788 (0·459–1·339)	0·38	18 (10·2%)	20 (19·8%)	0·463 (0·217–0·978)	0·0301
Component outcomes												
Surgical site infection (superficial incisional)	36 (6·4%)	36 (7·0%)	0·928 (0·558–1·543)	0·81	23 (6·0%)	20 (4·8%)	1·259 (0·649–2·461)	0·53	13 (7·4%)	16 (15·8%)	0·425 (0·179–0·992)	0·0399
Non-surgical-site infection	11 (2·0%)	23 (4·5%)	0·435 (0·189–0·940)	0·0238	6 (1·6%)	19 (4·6%)	0·331 (0·107–0·875)	0·0149	5 (2·8%)	4 (4·0%)	0·710 (0·149–3·666)	0·73
Wound separation	3 (0·5%)	8 (1·6%)	0·346 (0·059–1·453)	0·13	1 (0·3%)	6 (1·5%)	0·178 (0·004–1·480)	0·13	2 (1·1%)	2 (2·0%)	0·570 (0·041–7·979)	0·62
Seroma	5 (0·9%)	12 (2·3%)	0·383 (0·105–1·179)	0·09	3 (0·8%)	11 (2·7%)	0·290 (0·052–1·108)	0·06	2 (1·1%)	1 (1·0%)	1·149 (0·059–68·457)	1·00
Haematoma	1 (0·2%)	2 (0·4%)	0·466 (0·008–8·969)	0·61	0 (0·0%)	1 (0·2%)	..	..	1 (0·6%)	1 (1·0%)	0·573 (0·007–45·300)	1·00
Other	2 (0·4%)	1 (0·2%)	1·867 (0·097–110·358)	1·00	2 (0·5%)	1 (0·2%)	2·166 (0·112–128·141)	0·61	0 (0·0%)	0 (0·0%)	..	..

Significance was calculated with Fisher's exact test. *Adjusted odds ratio 0·658 (95% CI 0·438–0·988; p=0·0438 [calculated with Mantel-Haenszel test]).

Table 4: **Primary outcome and its components in modified intention-to-treat population**

(11·5%, 8·9–14·6), including 36 (7·0%, 5·0–9·6) with superficial incisional surgical site infections (table 4). As a primary outcome, the number of wound complications did not differ significantly between the two groups (OR 0·709, 95% CI 0·474–1·062; p=0·12). Since we identified confounding with the stratified factor, type of surgery, adjustment was done to show a significant difference (0·658, 0·438–0·988; p=0·0438), although this was not prespecified.

Post-hoc exploratory analyses showed that wound complications excepting surgical site infections occurred significantly less often in the subcuticular suture group than in the staples group overall (OR 0·435, 95% CI 0·189–0·940; p=0·0238) and in patients who underwent upper gastrointestinal surgery (0·331, 0·107–0·875; p=0·0149). In patients who underwent lower gastrointestinal surgery, significantly fewer wound complications (0·463, 0·217–0·978; p=0·0301) and superficial incisional surgical site infections (0·425, 0·179–0·992; p=0·0399) were noted in the subcuticular sutures than in the staples group (table 4).

Table 5 summarises secondary outcomes. Significantly fewer hypertrophic scars formed in the subcuticular sutures group than in the staples group overall (OR 0·726, 0·528–0·998; p=0·0429) and specifically in patients who underwent upper gastrointestinal surgery (0·672, 0·465–0·965; 0·0282).

We did a post-hoc subset analysis to identify potential interactions between wound complications and background factors (figure 2). Significant risk reduction for wound complications was noted with subcuticular sutures compared with staples in male patients (*vs* female patients), lower gastrointestinal surgery (*vs* upper gastrointestinal surgery), cases with operative time of 220 min or greater (*vs* those with operative times <220 min), and patients receiving postoperative anticoagulant therapy (*vs* those not receiving such therapy). We did not identify any important treatment-related adverse events for stapling or subcuticular sutures.

	n	Hypertrophic scar formation	Odds ratio (95% CI)	p
All patients			0·726 (0·528–0·998)	0·0429
Subcuticular sutures	558	93 (16·7%)		
Staples	514	111 (21·6%)		
Upper gastrointestinal surgery			0·672 (0·465–0·965)	0·0282
Subcuticular sutures	382	66 (17·3%)		
Staples	413	98 (23·7%)		
Lower gastrointestinal surgery			1·226 (0·576–2·729)	0·72
Subcuticular sutures	176	27 (15·3%)		
Staples	101	13 (12·9%)		

Data for hypertrophic scar formation are n (%). Significance was calculated with Fisher's exact test.

Table 5: **Secondary outcomes in the modified intention-to-treat population**

Discussion

Subcuticular sutures for skin closure have been advocated instead of staples in clean (class 1) surgery, including cardiovascular surgery,[24] orthopaedic surgery,[19] and caesarean delivery,[25] on the basis of the results of randomised studies. Whether these results can be applied to class 2 surgery, as represented by gastrointestinal surgery, is of concern. Classification of the types of surgery is described in panel 1. Our results show that subcuticular sutures did not significantly reduce the frequency of