論文の書き方

がん対策情報センター　臨床試験・診療支援部
JCOG データセンター
黒川　幸典

Topics of Today's Lecture

- 一流誌にアクセプトされやすい研究とは
- 論文執筆の基本原則
- Draft 執筆から論文が掲載されるまで
- 実際の論文作成の例

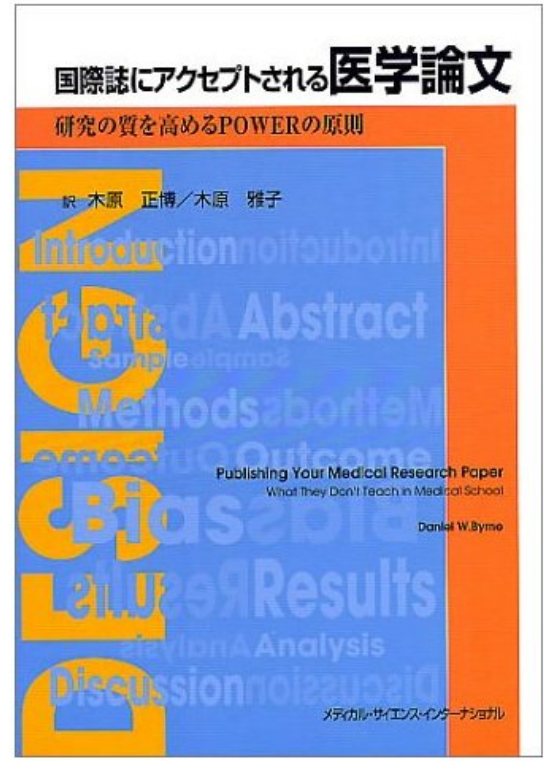
Tokai Univ. MCBS Program
Medical Writing Course (Daniel W. Byrne)

東海大学大学院 医学研究科
クリニカルバイオメディカル情報科学マスターコース

http://mcbs.med.u-tokai.ac.jp/mcbs/

Daniel W. Byrne
Senior Associate in Biostatistics
GCRC Director of Biostatistics and Study Design
Vanderbilt University School of Medicine
Department of Biostatistics

米国 Vanderbilt 大学総合臨床研究センターの統計部門ディレクタを務める。
同センターにおける臨床研究のデザイン・統計解析を精力的に支援しており、その成果は一流誌に多数発表され続けている。著書は、「国際誌にアクセプトされる医学論文：研究の質を高める POWER の原則」として翻訳され、我が国でも好評を博している。
同大学 Master of Science Clinical Investigation コースで、Biostatistics 1, Medical Writing を教えており、Best Teacher Award にも輝いている。



5 Phases of POWER Principles

- ***Planning***
- ***Observing***
- ***Writing***
- ***Editing***
- ***Revising***

Planning

Key Questions

- 知りたい research question は何か？
- その research question を解明するためには、どのような研究がふさわしいか？
- その研究は、患者さんにどういった利益をもたらすのか？

How Reviewers Define “A Good Article”

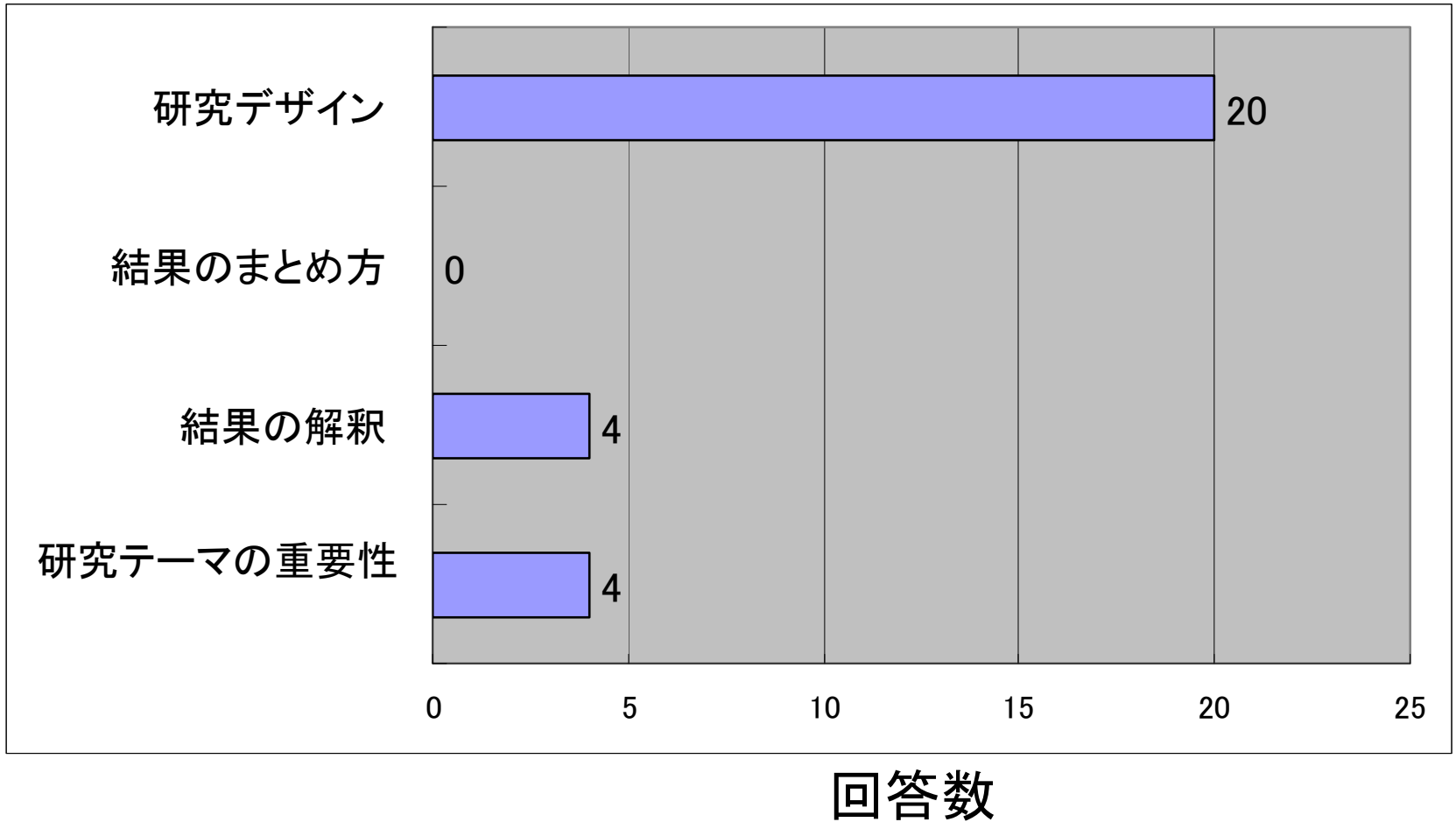
- 読者に「なぜ自分はこれを思いつかなかったのだろう」とうならせる論文
- 重要で興味深く、タイムリーなテーマを取り上げたもの
- 読者の興味に合い、臨床に関連が深いもの
- オリジナリティが高いもの
- 結果の再現性が高いもの
- まだ報告されたことのない研究テーマを適切なデザインで研究したもの
- 明快で読みやすく書かれ、読者に新しいアイデアを与えるもの

What is the single most common type of flaw that results in outright rejection of a manuscript?

- 1. 研究デザイン
- 2. 結果のまとめ方
- 3. 結果の解釈
- 4. 研究テーマの重要性

一流誌のeditors、JAMAのreviewers、ノーベル賞受賞者へのアンケート調査

The Most Common Type of Flaw



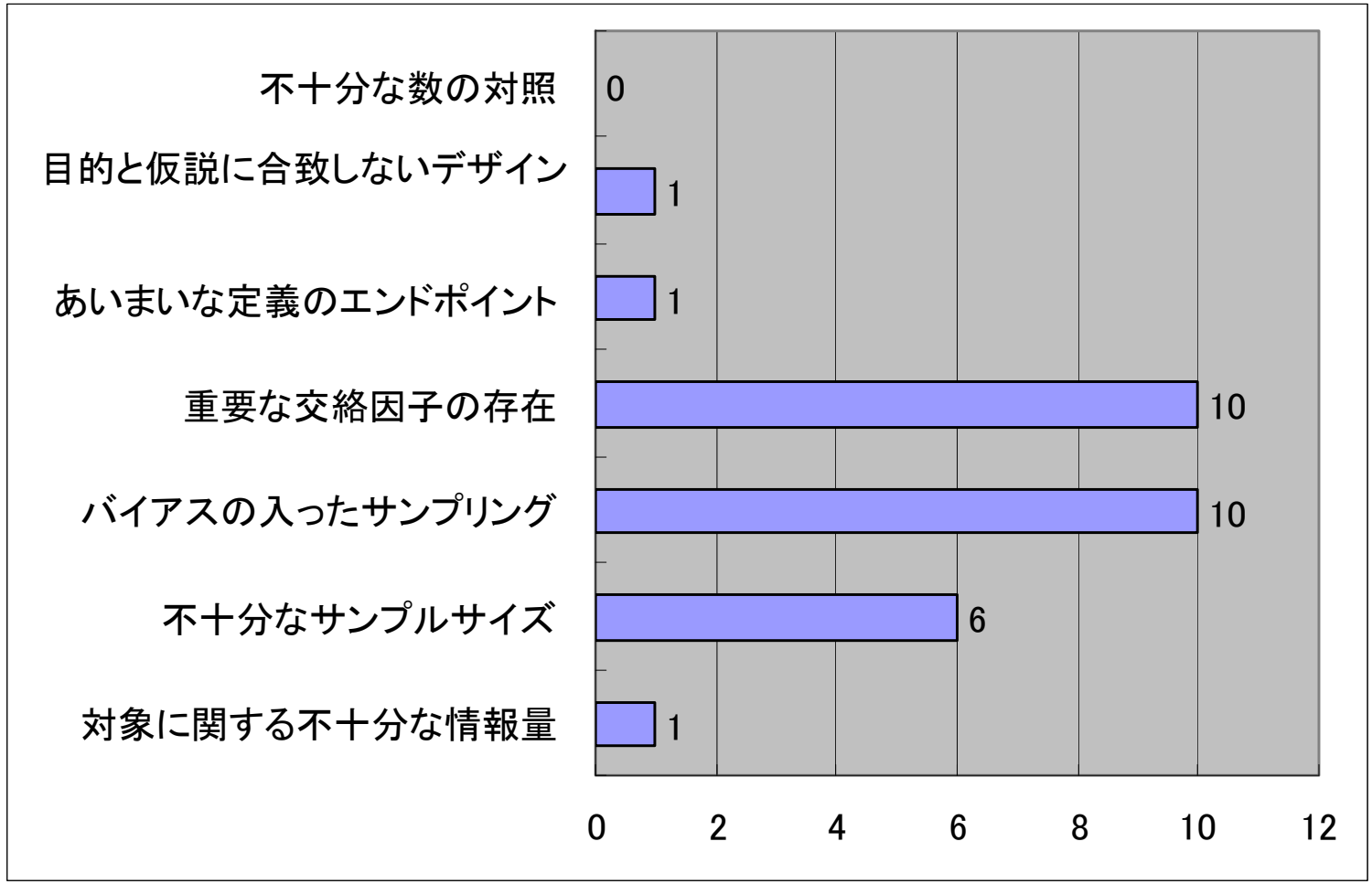
What is a good study design?

- 対象
  - 十分なサンプル数
  - 代表性、均一性の高い集団
  - 単施設 ＜ 多施設
- 介入
  - ランダム化
  - プラセボ対照
  - double or triple blinded
- 結果事象
  - 定義が明確
  - 特異性、客観性の高いアウトカム
  - 広く認められた測定法
  - 後向き ＜ 前向き

Of these 7 problems, which is most often responsible for outright rejection?

- 1. 不十分な数の対照
- 2. 研究の目的と仮説に合致しない研究デザイン
- 3. あいまいな定義のエンドポイント
- 4. 考慮されていない重要な交絡因子の存在
- 5. 信頼性を損なうようなバイアスの入ったサンプリング
- 6. 不十分なサンプルサイズ
- 7. 研究対象に関する不十分な情報量

The Most Common Type of Problem



Avoiding the Common Pitfalls

- 不適切な研究デザインは、reject の最大の原因
- データを収集する前に、研究デザインを再考すること
- 経験のある生物統計家に早い段階で相談すること

Specific Way to Improve the Study Design

- 交絡因子をどのように制御するかを検討する
- バイアスをどのように最小化するかを検討する
- データを収集する前に、必要なサンプルサイズと検出力を計算しておく
- コントロール群の設定をよく検討する

Data Collection Form

- データ収集用紙は、短くかつ包括的にする
- データ収集用紙の予備調査を行っておく
- 実際の統計解析を想定する
- データ収集用紙を事前に統計家にチェックしてもらう
- 交絡因子の項目も忘れずに

Writing

Sections of a Manuscript

- Title
- Abstract
- Introduction
- Methods
- Results
- Tables/Figures
- Discussion/Conclusions
- References
- Acknowledgment

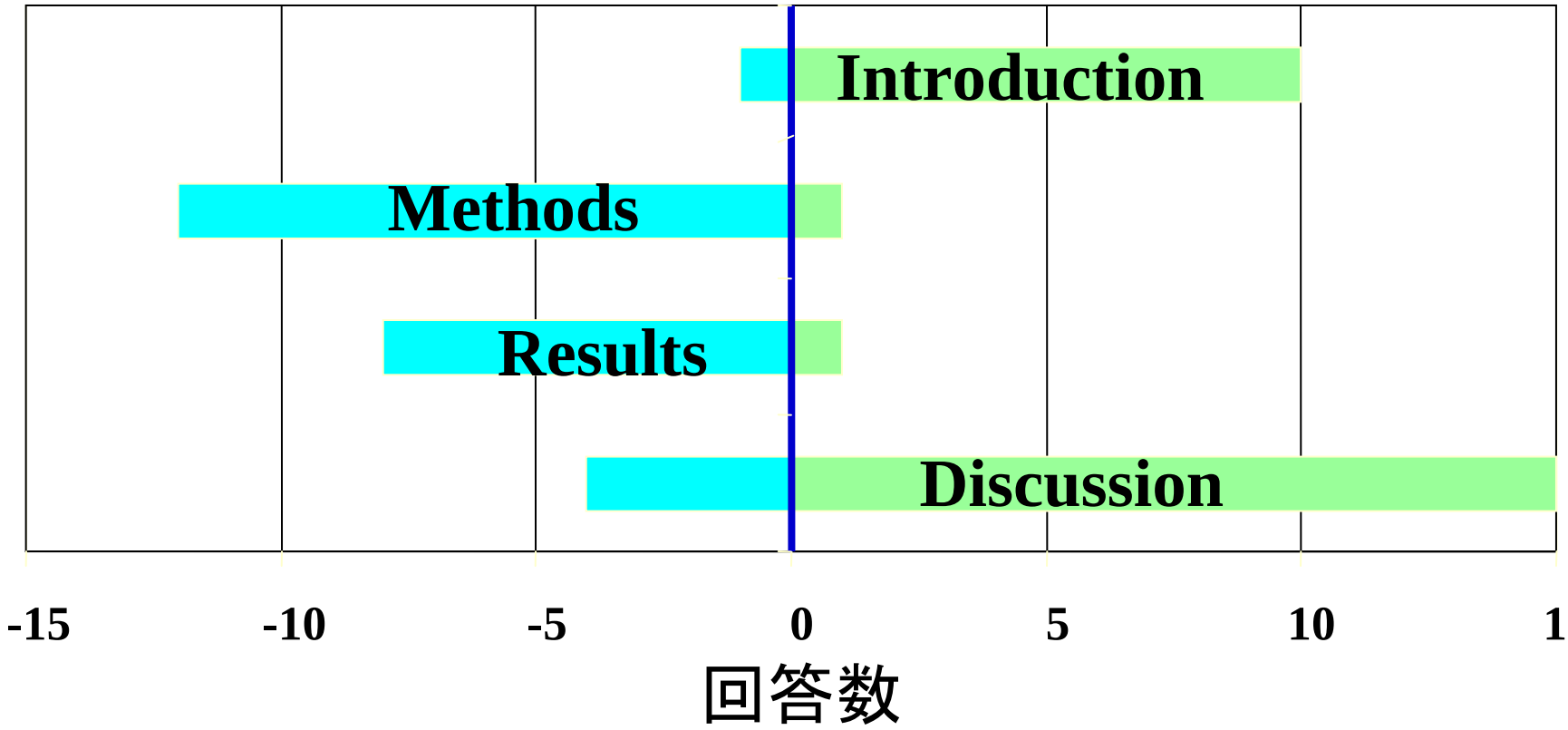
Key questions to answer in the writing phase

なぜこの研究を行ったのか？	Introduction
どのように研究を行ったのか？	Methods
この研究で何を見つけたのか？	Results
この結果は何を意味するのか？	Discussion

Which Section is Usually Too Short?
Which Section is Usually Too Long?

- Introduction
- Methods
- Results
- Discussion

Which Section is Usually Too Short?
Which Section is Usually Too Long?



Too Short **Too Long**

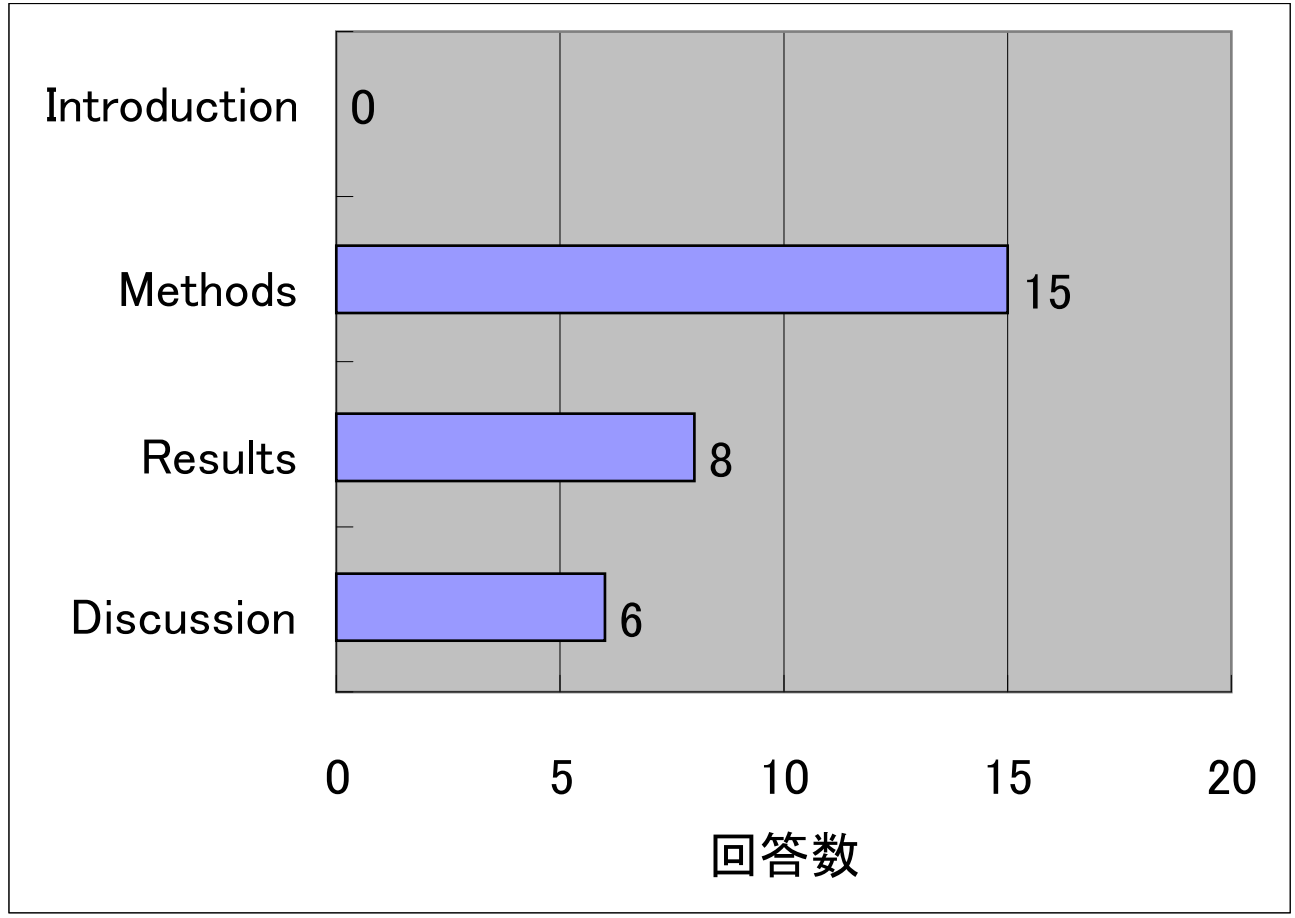
Avoiding the Common Pitfalls

- 真ん中の2つのセクションは、より長く書くこと
  - Methods – もっと詳細に
  - Results – 読者が納得するような結果を書く
- 他の2つのセクションは、より簡潔に書くこと
  - Introduction – 1ページ以内にまとめる
  - Discussion – ポイントを明確にし、文献のレビューばかりにしない

Which section is most often responsible for outright rejection of a paper?

- Introduction
- Methods
- Results
- Discussion

The Methods section is most often responsible for rejection

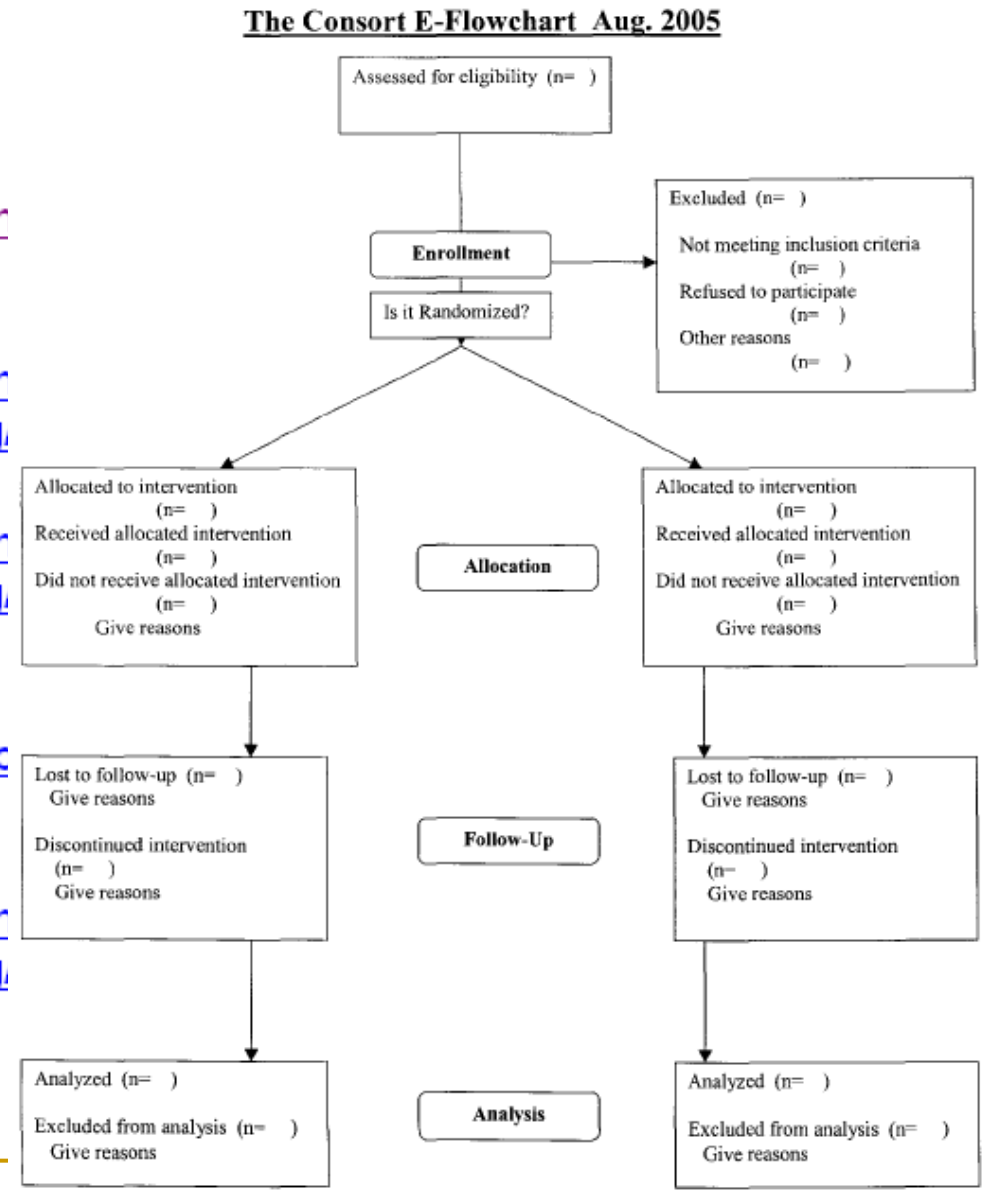


Guidelines

Initiative	Type of study	Source
CONSORT	randomized controlled trials	http://www.consort-statement.org
STARD	studies of diagnostic accuracy	http://www.consort-statement.org/stardstatement.htm
QUOROM	systematic reviews and meta-analyses	http://www.consort-statement.org/Initiatives/MOOSE/moose.pdf
STROBE	observational studies in epidemiology	http://www.strobe-statement.org
MOOSE	meta-analyses of observational studies in epidemiology	http://www.consort-statement.org/Initiatives/MOOSE/moose.pdf

Guidelines

Initiative	Type of study	Source
CONSORT	randomized controlled trials	http://www.cor
STARD	studies of diagnostic accuracy	http://www.cor statement.org
QUOROM	systematic reviews and meta-analyses	http://www.cor statement.org
STROBE	observational studies in epidemiology	http://www.stro
MOOSE	meta-analyses of observational studies in epidemiology	http://www.cor statement.org



ICMJE Statement

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication

Updated February 2006

International Committee of Medical Journal Editors

http://www.icmje.org/

Title Page

① **Title:** Risk Factors for mortality among patients hospitalized for hip fracture

② **Authors:** Yukinori Kurokawa, Seiichiro Yamamoto

③ The Japan Clinical Oncology Group (JCOG) Datacenter, Tokyo, Japan

④ **Running title:** Mortality following hip fracture

⑤ **Correspondence:** Yukinori Kurokawa, MD, PhD
The Japan Clinical Oncology Group (JCOG) Datacenter,
5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Tel/Fax: +81-3-3547-1002
E-mail: yukuroka@gan2.res.ncc.go.jp

⑥ Supported by Grants-in-Aid for Scientific Research on Priority Areas, Japan.

⑦ **Word count:** 1990

① タイトル

② 著者名

③ 施設名

④ 見出しタイトル

⑤ Corresponding author

⑥ 研究費の出所

⑦ 論文全体の語数

Title

- 興味を引くようなものにする
- 簡潔で短いこと（語数は10～12まで）
- 論文の結論までは述べない
- 研究デザインを示す
- キーワードで始まるものがよい
- 略語は用いない

What's Wrong With These Titles?

- A study of risk factors for anastomotic leakage and abdominal abscess after gastrectomy among gastric cancer patients with diabetes mellitus
  （糖尿病を有する胃がん患者に対する胃切除後の縫合不全および腹腔内膿瘍に関する危険因子の研究）

- Obesity is a risk factor for anastomotic leakage and abdominal abscess among gastric cancer patients with DM and HTN
  （糖尿病と高血圧を有する胃がん患者に対して、肥満は縫合不全や腹腔内膿瘍の危険因子である）

- Anastomotic leakage and abdominal abscess after gastrectomy
  （胃切除後の縫合不全と腹腔内膿瘍）

Authorship

- 真に研究に貢献した人のみを共著者とし、貢献していない人を共著者に加える（gift authorship）は望ましくない
- 最近の一流誌では、全ての共著者においてどのような貢献をしたのかを明記するよう要求される
- ICMJE が推奨する共著者の規準
  - 研究デザイン、データ収集、データ解析、解析結果の解釈、のいずれかを行った
  - 論文ドラフトを書いた、もしくは修正作業に加わった
  - 投稿論文の内容を承諾している

上記3つの条件を全て満たしていることが必要。

Abstract Page

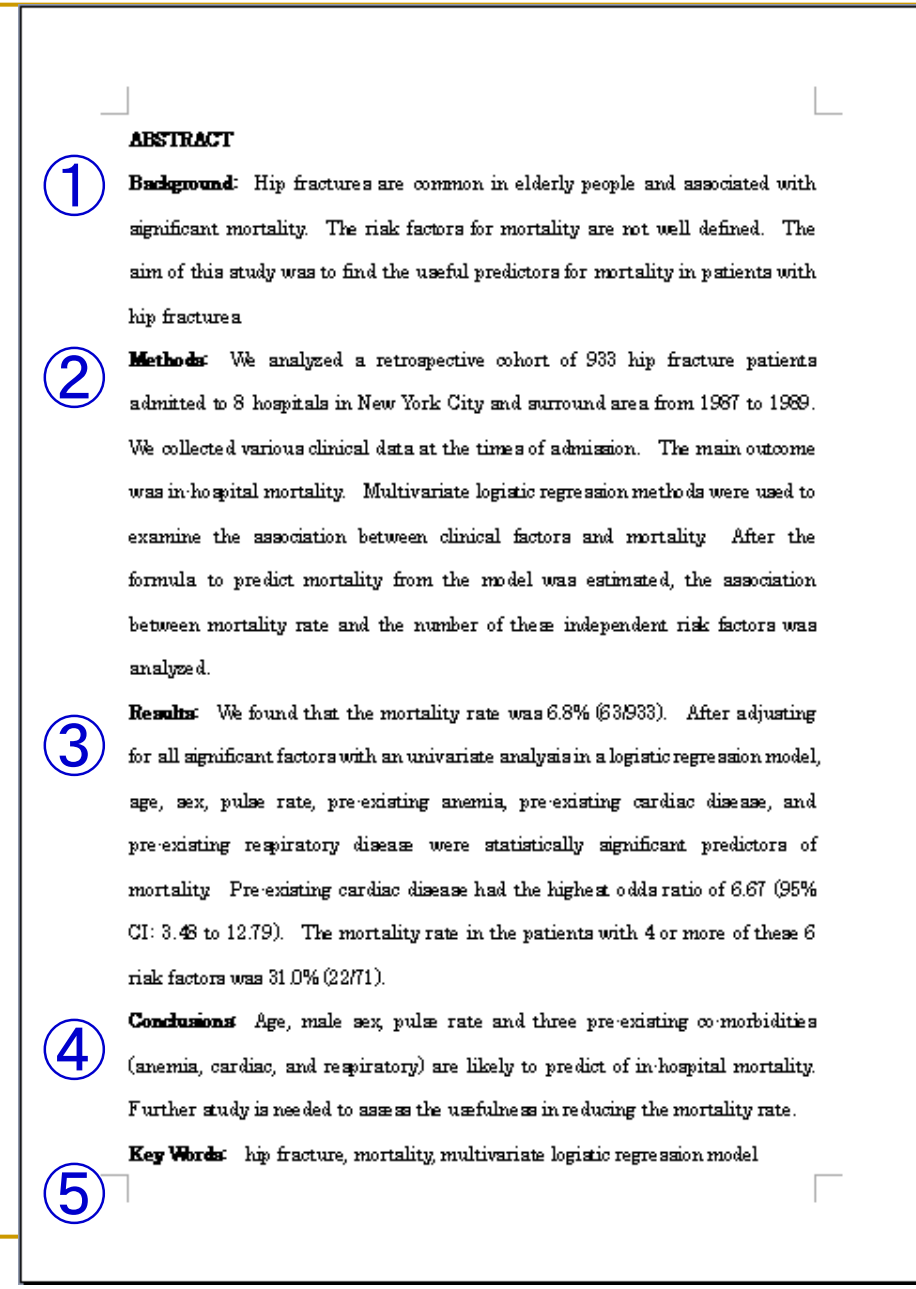
① Background

② Methods

③ Results

④ Conclusions

⑤ Key words



ABSTRACT

① **Background:** Hip fractures are common in elderly people and associated with significant mortality. The risk factors for mortality are not well defined. The aim of this study was to find the useful predictors for mortality in patients with hip fractures.

② **Methods:** We analyzed a retrospective cohort of 933 hip fracture patients admitted to 8 hospitals in New York City and surround area from 1987 to 1989. We collected various clinical data at the times of admission. The main outcome was in-hospital mortality. Multivariate logistic regression methods were used to examine the association between clinical factors and mortality. After the formula to predict mortality from the model was estimated, the association between mortality rate and the number of these independent risk factors was analyzed.

③ **Results:** We found that the mortality rate was 6.8% (63/933). After adjusting for all significant factors with an univariate analysis in a logistic regression model, age, sex, pulse rate, pre-existing anemia, pre-existing cardiac disease, and pre-existing respiratory disease were statistically significant predictors of mortality. Pre-existing cardiac disease had the highest odds ratio of 6.67 (95% CI: 3.48 to 12.79). The mortality rate in the patients with 4 or more of these 6 risk factors was 31.0% (22/71).

④ **Conclusions:** Age, male sex, pulse rate and three pre-existing co-morbidities (anemia, cardiac, and respiratory) are likely to predict of in-hospital mortality. Further study is needed to assess the usefulness in reducing the mortality rate.

⑤ **Key Words:** hip fracture, mortality, multivariate logistic regression model

Abstract

- 明快かつ簡潔にまとめる
- ほとんどの読者は Abstract しか読まないので、特に時間をかけてよいものを作る
- 投稿する雑誌の規定に合わせる
- 略語は用いない
- Conclusions は得られた結果から論理的に導けるものとし、保守的にまとめる

Introduction

① 最初に、この論文でどういうテーマに取り組もうとしているか（研究目的）を述べる

② 次に、その背景となる文献を引用する

③ 過去に報告された研究と自分の研究との違いを示し、この研究のデザインを述べる

④ 最後に、この研究によってどのような臨床的意義があるのかを述べる

Introduction

- 出だしの文章は、読者を引きつけられるよう工夫する
- 冗長にならないよう、簡潔にまとめる（1ページ程度）
- 引用する文献は、この研究ともっとも関連したものだけに絞る
- Introduction には、データを載せない
- Introduction には、結論も書かない

Methods

① 適格規準と除外規準
② サンプルサイズ計算
③ 用いる変数の定義
④ エンドポイントの定義
⑤ 研究の開始時期と終了時期
⑥ データの収集情報（誰が、いつ、どこで、どのように）
⑦ 解析に使用したソフトウェア
⑧ インフォームドコンセント、IRB 承認

Methods

- より長く詳細に書くようにする（3～4ページ）
- 適切な小見出しをつけて読みやすくする
- 同じ研究を他の研究者が再現できるよう記載する（料理のレシピと同様）
- 適格規準でポイントとなる部分については、その設定根拠も書く
- 統計解析の部分は1ページ程度は書く
- なぜその統計解析を用いたかの根拠を示す
- Methods のセクションにて、著者の科学的な skill をアピールできるように努力する

Results

① 最初に、この研究実施がどの程度うまくいっているかを示す

- 収集したデータ全体の概要
- RCT であれば、CONSORT のフローチャート

② 次に、背景因子の比較

③ そして、単変量解析の結果

④ 最後に、多変量解析の結果というパターンが多い

Results

- データを自然な順序で記述する
- 結果だけを書き、考察は書かない
- データの欠測がある場合には、その理由およびいくつ不完全なデータがあったのかを正確に記載する
- 95%信頼区間を必ず記載する
- P値はできるだけ実数で表示する
  - $P < 0.001$ の時は、”$P < 0.001$” だけで十分
  - $0.001 \leq P < 0.10$ の時は、小数点以下第3位まで
  - $P \geq 0.10$ の時は、小数点以下第2位まで

Results

- 同じデータを、表と本文の両方で繰り返さない
- 本文中に、すべての表と図を引用し、その内容を要約する
- 質の高い表を作る
  - 個々の変数には単位を明記
  - 縦線は用いない
- サンプルサイズの小さな研究では、個々の症例の主な変数を一覧表の形で示す
- グラフ化するのは、主な知見、しかもテキストや表では表現しにくいものにとどめる
- 重要な連続変数については、その分布特性を調べるためヒストグラムか折れ線グラフを作る

Discussion

① Discussion は、もっとも重要なポイントから始める
- だらだらとした前置きは不要
- Introduction で引用した文献は二度引用しない

② 研究結果の解釈を行い、文献に見られる結果と自分の結果をよく比較する
- 他の文献の批判は最小限にとどめる

③ 結果の別の解釈についても論じる

④ この研究の限界（limitation）を論じる

⑤ この研究結果の臨床的意義を述べる

⑥ 最後に、力強く明快な結論で締めくくる

Discussion

- 主要なテーマに絞った議論を展開し、簡潔にまとめる
- Results の中に書かれていないデータを論じない
- その研究で得られた新しい知見（ノイエス）が何であるかを明確にする
- 他の文献の review 的コメントは書かない
- Reviewer のあら探しに備えて先にコメントしておく
- 推論は行き過ぎないこと
- 誇張された表現は使わず控えめに
- 将来どのような研究が必要であるかを述べる
- 結論は十分なデータに裏付けられた慎重なものにする

Acknowledgement

- ICMJE による Authorship criteria を全ては満たしていないが、研究に協力してくれた人の名前を載せる。
  - Technical help
  - Writing assistance
  - Department chair who provided only general support
- Financial support
- Material support

References

- 重要な文献は、たとえ自分の研究にとって negative な場合であっても必ず引用すること
- 投稿規定に従って文献を引用する
  - 上付き文字、丸括弧、角括弧など様々
  - 共著者名を何人まで記載するか
- アクセプトされ印刷待ちの論文は引用できる
  - 雑誌の巻号やページの代わりに“(in press)”と書いておく
- 学会抄録も雑誌に掲載されたものであれば引用できる

Editing

Editing Process

- First drafting

- Internal peer review

- Native check

- Final draft with cover letter

- Online/Manual submission

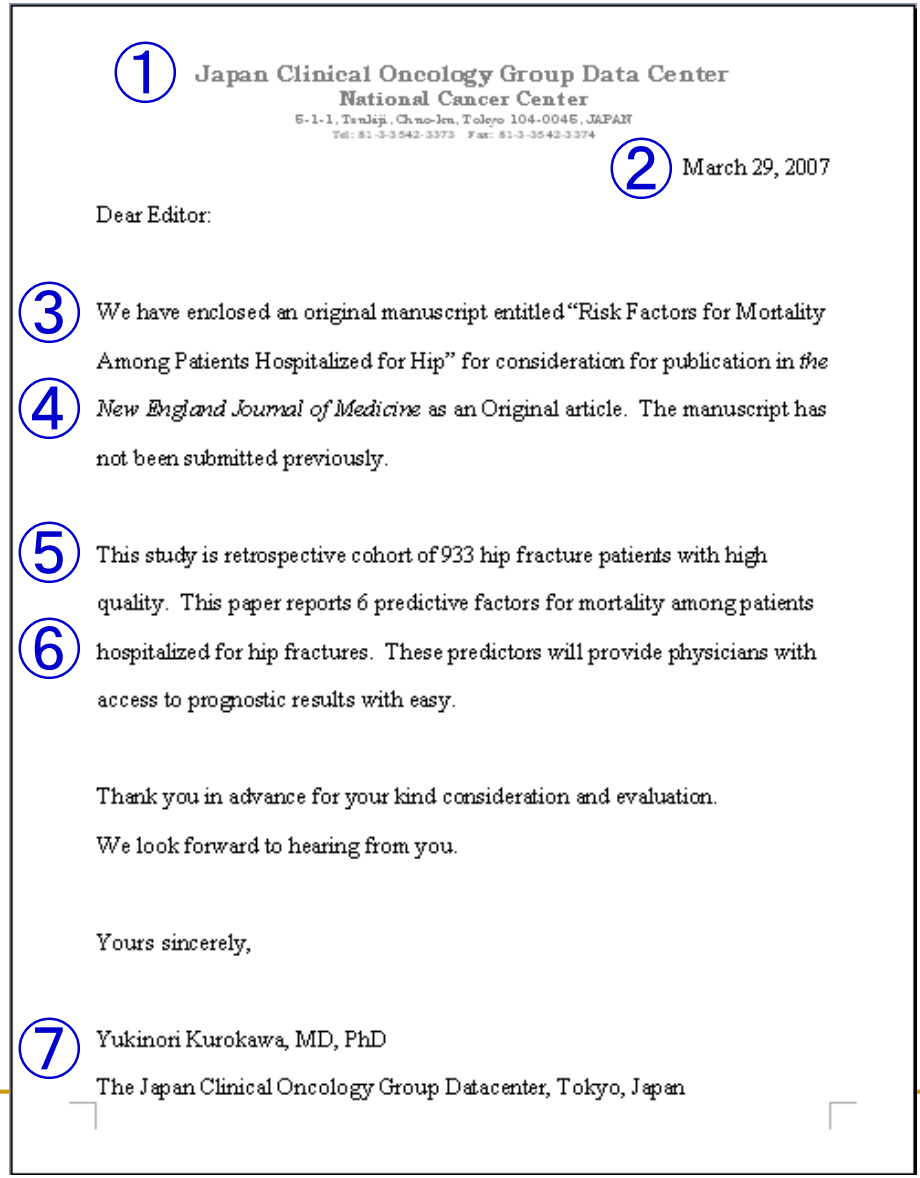
- ダブルスペースで書く（A4 12pt.で23行）
  - 文章を全て選択して、Ctrl ボタンを押しながら “2“ を押す
- できるだけ文を数字で始めない
  - “One hundred ninety-seven patients …”
- 単位が付いていない10未満の数字は、アルファベットで綴るのが原則
- やたらとカンマ（“ ”）やダッシュ（-）を用いるのは避ける
- 言葉や句を羅列する場合には、セミコロン（;）を使う
  - “Eligibility criteria were as follows: (1) _; (2) _; and (3) _.”
- 記号は半角のみを使う
  - ≧ → ≥
- ピリオド（.）とコロン（:）の後は半角で2スペース、セミコロン（;）の後は半角で1スペース空ける

- 短い文を作るよう心がける
- 能動態で書けるときには、受動態を使わない
- “There”で始まる文章はできるだけ書き直す
  - “There were no leakages or abdominal abscesses.”

    → “No leakages or abdominal abscesses occurred.”
- “It”で始まる文章はできるだけ書き直す
  - “It was important to freeze samples to ensure accuracy.“

    → “Freezing samples was important to ensure accuracy.“
- ハイフン（-）は、付けないと意味を間違いやすい場合に限る
  - 付ける例：　all-　　cross-　　self-　　数字　　分数
  - 付けない例：
    - multi-center → multicenter
    - non-smoker → nonsmoker
    - post-operative → postoperative

Cover Letter



① Japan Clinical Oncology Group Data Center
National Cancer Center
6-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, JAPAN
Tel: 81-3-3542-3373 Fax: 81-3-3542-3374

② March 29, 2007

Dear Editor:

③ We have enclosed an original manuscript entitled "Risk Factors for Mortality Among Patients Hospitalized for Hip" for consideration for publication in *the New England Journal of Medicine* ④ as an Original article. The manuscript has not been submitted previously.

⑤ This study is retrospective cohort of 933 hip fracture patients with high quality. This paper reports 6 predictive factors for mortality among patients ⑥ hospitalized for hip fractures. These predictors will provide physicians with access to prognostic results with easy.

Thank you in advance for your kind consideration and evaluation.

We look forward to hearing from you.

Yours sincerely,

⑦ Yukinori Kurokawa, MD, PhD

The Japan Clinical Oncology Group Datacenter, Tokyo, Japan

① 自施設のヘッダー

② 日付

③ 論文タイトル

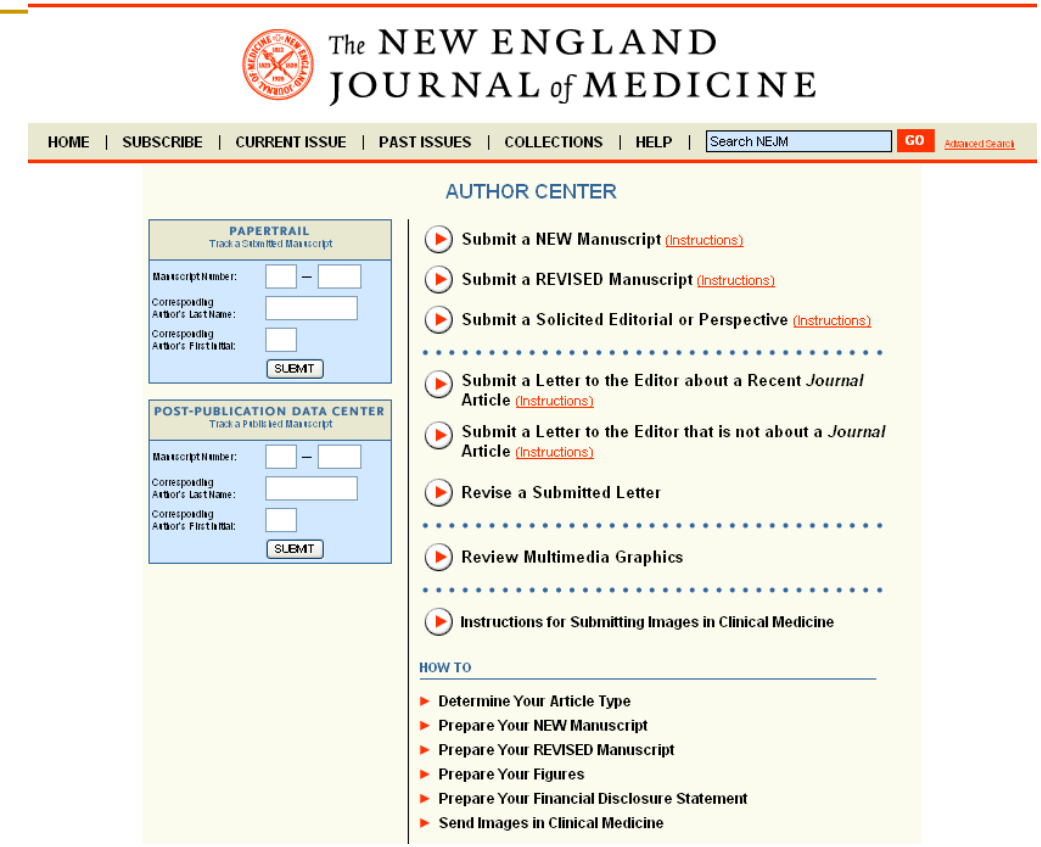
④ Journal名

⑤ 研究テーマ

⑥ アピールポイントを一言で

⑦ 自分の名前
（corresponding author)

Submission



- Target audience の興味に合致した雑誌を選ぶこと
- 投稿する雑誌の投稿規定を再確認する
- 回してほしい reviewer や
  回してほしくない reviewer を指名することができる
- 当たればもうけもの的な雑誌から投稿するか、それともちょうど狙い目と考えられる雑誌から投稿するか？

Revising

Evaluation System

- 採否を決めるのは、Editor-in-chief または担当した Editor であり、Reviewer ではない
- Editor に指名された Reviewer は論文の評価を書いて送り返す（スコアを付けて返す場合も多い）
- Reviewer の数は雑誌によって様々だが、審査の途中で追加されることもある
- 審査結果
  - Accept
  - Minor Revision
  - Major Revision
  - Reject

Responding to Reviewers Comments

- 決して怒らない
- 最大のゴールは論文の accept を勝ち取ることなので、Editor や Reviewer が理不尽なことを言ってきても、できるだけ丁寧な対応をとる
- 再投稿する場合は、指定された期限内、しかもできるだけ迅速に対応する
- 他の雑誌に投稿する場合は、気持ちが萎えないうちに、すぐに指摘された問題点を修正して投稿する
- どこかに accept されるまでは、絶対に諦めない！

Response Letter

- 最初に、Editor への手紙を書き、次のページから各 Reviewer のコメントに対する回答を書く
- Reviewer のコメントの中で受け入れられるものについては、どのように修正したかを回答する
- 受け入れられないコメントについては、なぜ受け入れられないかを説明する
- それぞれどのコメントに対応する回答なのかを明示し、修正原稿の該当するページ数と行数も書く
- Editor や Reviewer の suggestion に感謝の意を表す

実際の論文作成の例

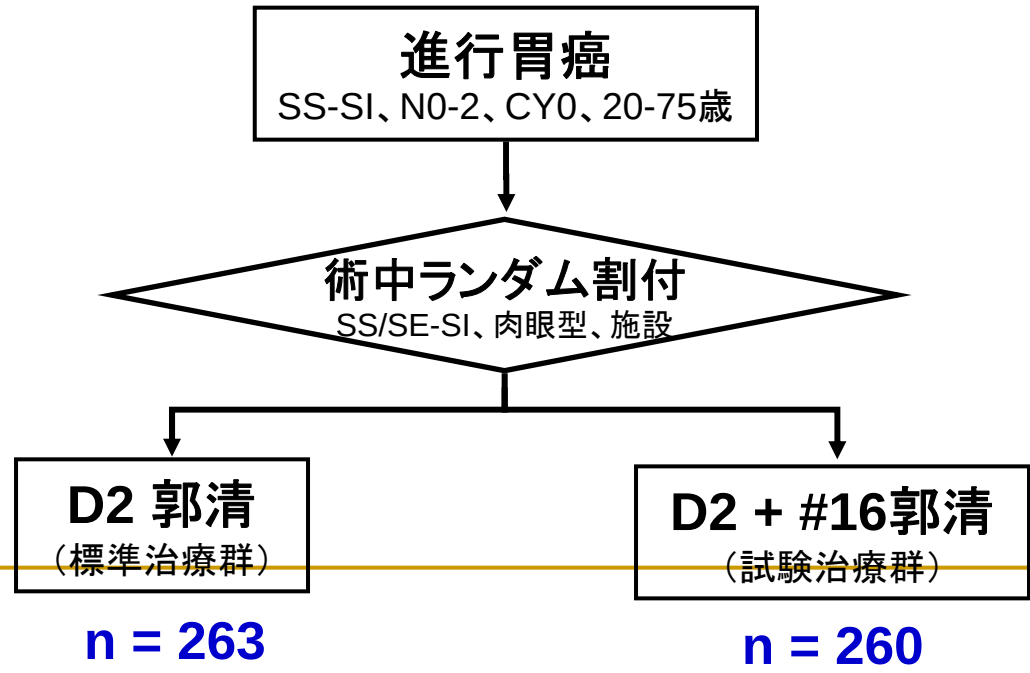
Annals of Surgical Oncology 14(2):355–361
DOI: 10.1245/s10434-006-9209-3

Influence of Overweight on Surgical Complications for Gastric Cancer: Results From a Randomized Control Trial Comparing D2 and Extended Para-aortic D3 Lymphadenectomy (JCOG9501)

Toshimasa Tsujinaka, MD,[1] Mitsuru Sasako, MD,[2] Seiichiro Yamamoto, PhD,[3] Takeshi Sano, MD,[2] Yukinori Kurokawa, MD,[3] Atsushi Nashimoto, MD,[4] Akira Kurita, MD,[5] Hitoshi Katai, MD,[2] Toshio Shimizu, MD,[6] Hiroshi Furukawa, MD,[7] Satoru Inoue, MD,[8] Masahiro Hiratsuka, MD,[9] Taira Kinoshita, MD,[10] Kuniyoshi Arai, MD,[11] and Yoshitaka Yamamura, MD,[12] for the Gastric Cancer Surgery Study Group of Japan Clinical Oncology Group

New Theme

- JCOG9501（胃癌に対するリンパ節郭清範囲のRCT）のデータを使って、BMI と合併症の関係を調べたい
  - 太った人は手術の合併症が増える？
  - 手術法によって、合併症に対する肥満の影響が違う？



Definition

- BMI をどこで分けるか？
  - 平均値？　中央値？　3分位点？
  - 臨床的に意味のある値？
    - 25以上が”Overweight”　→　9501では、523人中77人（15%）
    - 30以上が”Obesity”　→　9501では、523人中5人（1%）

- エンドポイントは？
  - 再手術の有無、在院死、全合併症、外科的合併症、縫合不全、膵液瘻、腹腔内膿瘍、術後肺炎
  - 手術時間、出血量、輸血の有無、リンパ節郭清個数は？

Preliminary Analysis- 1

- 背景因子の比較
  - 本来P値は不要
  - 両群間で大きな偏りがないことを確認
  - 偏りがあれば調整が必要

TABLE 1. *Backgrounds of patients according to body mass index (BMI)*

Factor	BMI < 25 (n = 446)	BMI ≥ 25 (n = 77)	Total number	*P* value
Sex				
M	301	57	358	.26
F	145	20	165	
Age				
< 56	137	23	160	.93
56–65	176	31	207	
> 65	133	23	156	
Location				
A (lower third)	188	29	217	.59
M (middle third)	173	33	206	
C (upper third)	85	15	100	
Clinical tumor stage				
cT2b	161	31	192	.38
cT3	268	41	309	
cT4	17	5	22	
Lymph node dissection				
D2	225	38	263	.86
D3	221	39	260	
Type of gastrectomy				
Distal	272	48	320	.82
Total/proximal	174	29	203	
Splenectomy				
No	283	49	332	.98
Yes	163	28	191	
Pancreatectomy				
No	427	74	501	.88
Yes	19	3	22	

Preliminary Analysis- 2

- 単変量解析
  - 統計的有意差が見られた因子
    - 全合併症
    - 外科的合併症
    - 膵液瘻
    - 腹腔内膿瘍
    - 手術時間
    - 出血量
    - リンパ節郭清個数

			Univariate analysis	
Factors	BMI < 25	BMI ≥ 25	Odds ratio of BMI > 25 (95% CI)	*P* value
Operation time (min)				
> 297	141	36	1.90 (1.16–3.10)	.01
≤297	305	41	–	
Blood loss (mL)				
> 710	131	44	3.21 (1.95–5.26)	< .001
≤710	315	33	–	
Blood transfusion				
Yes	98	17	1.01 (.56–1.80)	.98
No	348	60	–	
No. of retrieved lymph nodes				
≤54	137	33	1.69 (1.03–2.77)	.037
> 54	309	44	–	
Reoperation				
Yes	9	3	1.97 (.52–7.44)	.32
No	437	74	–	
Hospital death				
Yes	3	1	1.94 (.20–18.92)	.56
No	443	76	–	
Any complication				
Yes	101	27	1.84 (1.10–3.10)	.021
No	345	50	–	
Surgical complication				
Yes	34	15	2.93 (1.51–5.69)	.002
No	412	62	–	
Anastomotic leak				
Yes	8	3	2.22 (.58–8.56)	.25
No	438	74	–	
Pancreatic fistula				
Yes	20	10	3.18 (1.43–7.09)	.005
No	426	67	–	
Abdominal abscess				
Yes	19	10	3.35 (1.50–7.52)	.003
No	427	67	–	
Pneumonia				
Yes	12	4	1.98 (.62–6.31)	.25
No	434	73	–	
Other complication				
Yes	65	11	0.98 (.49–1.95)	.95
No	381	66	–	

Preliminary Analysis- 3

- 多変量解析
  - 統計的有意差が見られた因子
    - 全合併症
    - 外科的合併症
    - 膵液瘻
    - 腹腔内膿瘍
    - 手術時間
    - 出血量
    - リンパ節郭清個数

			Multivariate analysis	
Factors	BMI < 25	BMI ≥ 25	Odds ratio of BMI > 25 (95% CI)	*P* value
Operation time (min)				
> 297	141	36	2.24 (1.29–3.87)	.004
≤297	305	41	–	
Blood loss (mL)				
> 710	131	44	3.74 (2.19–6.39)	<.001
≤710	315	33	–	
Blood transfusion				
Yes	98	17	1.10 (.59–2.03)	.77
No	348	60	–	
No. of retrieved lymph nodes				
≤54	137	33	1.82 (1.06–3.14)	.031
> 54	309	44	–	
Reoperation				
Yes	9	3	1.85 (.47–7.29)	.38
No	437	74	–	
Hospital death				
Yes	3	1	1.96 (.20–19.50)	.56
No	443	76	–	
Any complication				
Yes	101	27	1.90 (1.11–3.24)	.019
No	345	50	–	
Surgical complication				
Yes	34	15	3.35 (1.65–6.78)	<.001
No	412	62	–	
Anastomotic leak				
Yes	8	3	2.14 (.54–8.47)	.28
No	438	74	–	
Pancreatic fistula				
Yes	20	10	4.18 (1.71–10.22)	.002
No	426	67	–	
Abdominal abscess				
Yes	19	10	3.51 (1.52–8.12)	.003
No	427	67	–	
Pneumonia				
Yes	12	4	1.88 (.58–6.13)	.29
No	434	73	–	
Other complication				
Yes	65	11	0.97 (.48–1.95)	.93
No	381	66	–	

Preliminary Analysis- 4

- サブグループ解析
  - D2群では、BMI が大きいほど合併症のリスク高い
  - D3群では、BMI と合併症の関連性は低い

Factor	D2 subgroup (n = 263) Multivariate odds ratio of BMI ≥ 25 (95% CI)	D2 subgroup (n = 263) *P* value	D3 subgroup (n = 260) Multivariate odds ratio of BMI ≥ 25 (95% CI)	D3 subgroup (n = 260) *P* value	Interaction *P* value
Operation time					
Operation time > 297 min	2.19 (.96–5.02)	.063	2.27 (1.09–4.73)	.028	.95
Blood loss > 710 mL	2.83 (1.33–6.04)	.007	5.05 (2.27–11.26)	< .001	.30
Blood transfusion	1.73 (.70–4.26)	.23	0.78 (.34–1.79)	.56	.20
No. of retrieved lymph nodes ≤54	2.73 (1.28–5.85)	.01	1.06 (.43–2.62)	.9	.12
Reoperation	4.21 (.64–27.61)	.13	0.82 (.09–7.39)	.86	.27
Hospital death	6.82 (.40–117.43)	.19	NE	.98	.94
Any complication	2.62 (1.23–5.61)	.013	1.39 (.65–2.98)	.4	.25
Surgical complications	4.20 (1.59–11.10)	.004	2.60 (.91–7.40)	.074	.51
Anastomotic leak	2.77 (.47–16.19)	.26	1.49 (.16–14.09)	.73	.67
Pancreatic fistula	4.74 (1.42–15.89)	.012	3.61 (.96–13.55)	.057	.77
Abdominal abscess	4.72 (1.49–14.99)	.009	2.55 (.73–8.85)	.14	.48
Pneumonia	2.81 (.79–10.04)	.11	NE	.97	.94
Other complications	1.08 (.34–3.37)	.9	0.91 (.37–2.23)	.83	.82

Which Section Should be Written First?

1. Methods
2. Results
3. Introduction
4. Discussion

Methods Section- 1

- Between June 1995 and April 2001, 523 patients registered in the JCOG 9501 study were randomly allocated to either D2 (n=263) or D3 dissection (n=260) by balancing the groups according to institution, tumor growth pattern (expansive *v* infiltrative growth) and T stage (cT2b *v* cT3/cT4). Patients aged less than 76 years of age with histologically proven and resectable primary gastric carcinoma with an estimated depth of SS (invading subserosa: cT2b), SE (penetrating serosa: cT3) or SI (invading adjacent structures: cT4) were recruited after giving informed consent as described before in details. Patients with positive for free cancer cells by cytological examination of peritoneal washes and those with type 4 tumours (linitis plastica type) were excluded.

Methods Section- 2

- Patients underwent appropriate gastrectomy with systematic lymphadenectomy as allocated. Perigastric lymph nodes (nodal stations No.1, 3, 4, 5 and 6 according to the Japanese Classification of Gastric Cancer) and nodes at the base of the left gastric artery (No.7), along the common hepatic artery (No.8) and at the base of the splenic artery (No.11) were routinely resected …..

Methods Section- 3

- Information on complications (including major surgical complications) and patient backgrounds (including height and body weight) was extracted from the case report forms for the trial. In this study, anastomotic leakage, pancreatic fistula, and abdominal abscess are defined as surgical complications. Anastomotic leakage was defined as dehiscence confirmed by radiographic examination using contrast medium. Pancreatic fistula was diagnosed if there was prolonged purulent discharge that contained pancreatic juice from the drainage tube. In addition, pneumonia and other complications were considered as complications.

Methods Section- 4

- According to the World Health Organization classification, BMI≥25 was considered as being overweight (increased BMI) and BMI<25 as being non-overweight. Factors that might affect the risk of overall and major surgical complications, such as sex, age, tumor location, pathological (p) T category (pT2 and pT3 *v* pT4), extent of lymphadenectomy, type of gastrectomy, splenectomy and pancreatectomy were evaluated as potential confounding factors. The difference in the distribution of these factors between BMI<25 and BMI≥25 were examined by chisquared test. The effect of increased BMI on the complications was evaluated by the odds ratios. In addition, the effect of increased BMI on operative time, amount of blood loss, need for allogeneic blood transfusion, reoperation, and hospital death was also evaluated by the odds ratio.

Methods Section- 5

- Operative time, blood loss and the number of retrieved lymph nodes were divided into tertiles as previously described, and used as binary variables by dichotomizing the highest tertiles and the remaining two tertiles because biological meaningful cut off points could not be defined. In addition to the univariate analysis, all the analyses were conducted adjusting all the potential confounding factors by logistic regression.
- To see the difference of the effect of increased BMI between D2 and D3 dissection, all the analyses were repeated separately for D2 and D3 subgroup, and the interaction was also evaluated. All the statistical analysis was performed with the software SAS® version 8.12 (SAS Institute, Tokyo, Japan). P values less than 0.05 were considered statistically significant and all tests were two-sided.

Results Section- 1

- Seventy-seven patients were clas
  BMI≥25, and 38 and 39 of these
  lymphadenectomy, respectively.
  being non-overweight with BMI<2
  received D3 lymphadenectomy.
  performed in 199 (38.0%) of 523
  gastrectomy in four; the remainin
  gastrectomy. Splenectomy was
  (36.5%) and distal pancreatecton
  background characteristics of pat
  shown in Table 1. There were nc
  age, tumor location, clinical T sta
  of gastrectomy and incidence of
  the two groups, and the two grou

TABLE 1. *Backgrounds of patients according to body mass index (BMI)*

Factor	BMI < 25 (n = 446)	BMI ≥ 25 (n = 77)	Total number	*P* value
Sex				
M	301	57	358	.26
F	145	20	165	
Age				
< 56	137	23	160	.93
56–65	176	31	207	
> 65	133	23	156	
Location				
A (lower third)	188	29	217	.59
M (middle third)	173	33	206	
C (upper third)	85	15	100	
Clinical tumor stage				
cT2b	161	31	192	.38
cT3	268	41	309	
cT4	17	5	22	
Lymph node dissection				
D2	225	38	263	.86
D3	221	39	260	
Type of gastrectomy				
Distal	272	48	320	.82
Total/proximal	174	29	203	
Splenectomy				
No	283	49	332	.98
Yes	163	28	191	
Pancreatectomy				
No	427	74	501	.88
Yes	19	3	22	

Results Section- 2

- Any complications were identifie
  major surgical complications occ
  the entire study sample. Among
  the proportion developing either
  were 35.1% and 19.5%, respecti
  univariate analysis, increased BI
  risk for pancreatic fistula, abdom
  and blood loss (Table 2). Additic
  lymph nodes was significantly le

			Univariate analysis	
Factors	BMI < 25	BMI ≥ 25	Odds ratio of BMI > 25 (95% CI)	*P* value
Operation time (min)				
> 297	141	36	1.90 (1.16–3.10)	.01
≤297	305	41	–	
Blood loss (mL)				
> 710	131	44	3.21 (1.95–5.26)	< .001
≤710	315	33	–	
Blood transfusion				
Yes	98	17	1.01 (.56–1.80)	.98
No	348	60	–	
No. of retrieved lymph nodes				
≤54	137	33	1.69 (1.03–2.77)	.037
> 54	309	44	–	
Reoperation				
Yes	9	3	1.97 (.52–7.44)	.32
No	437	74	–	
Hospital death				
Yes	3	1	1.94 (.20–18.92)	.56
No	443	76	–	
Any complication				
Yes	101	27	1.84 (1.10–3.10)	.021
No	345	50	–	
Surgical complication				
Yes	34	15	2.93 (1.51–5.69)	.002
No	412	62	–	
Anastomotic leak				
Yes	8	3	2.22 (.58–8.56)	.25
No	438	74	–	
Pancreatic fistula				
Yes	20	10	3.18 (1.43–7.09)	.005
No	426	67	–	
Abdominal abscess				
Yes	19	10	3.35 (1.50–7.52)	.003
No	427	67	–	
Pneumonia				
Yes	12	4	1.98 (.62–6.31)	.25
No	434	73	–	
Other complication				
Yes	65	11	0.98 (.49–1.95)	.95
No	381	66	–	

Results Section- 3

- Multivariate analysis identified t
  significantly associated with pa
  abscess, operative time and blo
  were 4.18 (95% CI, 1.71-10.22)
  (95% CI, 1.29-3.87) and 3.74 (9
  The number of retrieved lymph
  patients with an odds ratio of 1.
  operative time and blood loss w
  factors, the odds ratios for the c
  and abdominal abscess decrea
  respectively, but were still statis

			Multivariate analysis	
Factors	BMI < 25	BMI ≥ 25	Odds ratio of BMI > 25 (95% CI)	*P* value
Operation time (min)				
>297	141	36	2.24 (1.29–3.87)	.004
≤297	305	41	–	
Blood loss (mL)				
>710	131	44	3.74 (2.19–6.39)	<.001
≤710	315	33	–	
Blood transfusion				
Yes	98	17	1.10 (.59–2.03)	.77
No	348	60	–	
No. of retrieved lymph nodes				
≤54	137	33	1.82 (1.06–3.14)	.031
>54	309	44	–	
Reoperation				
Yes	9	3	1.85 (.47–7.29)	.38
No	437	74	–	
Hospital death				
Yes	3	1	1.96 (.20–19.50)	.56
No	443	76	–	
Any complication				
Yes	101	27	1.90 (1.11–3.24)	.019
No	345	50	–	
Surgical complication				
Yes	34	15	3.35 (1.65–6.78)	<.001
No	412	62	–	
Anastomotic leak				
Yes	8	3	2.14 (.54–8.47)	.28
No	438	74	–	
Pancreatic fistula				
Yes	20	10	4.18 (1.71–10.22)	.002
No	426	67	–	
Abdominal abscess				
Yes	19	10	3.51 (1.52–8.12)	.003
No	427	67	–	
Pneumonia				
Yes	12	4	1.88 (.58–6.13)	.29
No	434	73	–	
Other complication				
Yes	65	11	0.97 (.48–1.95)	.93
No	381	66	–	

Results Section- 4

- We next analyzed the D2 (n=263) and D3 (n=260) dissection subgroups (Table 3). In the D2 subgroup, increased BMI was significantly associated with pancreatic fistula, abdominal abscess and blood loss with odds ratios of 4.74 (95% CI, 1.42-15.89), 4.72 (95% CI, 1.49-14.99) and 2.83 (95% CI, 1.33-6.04),

	D2 subgroup (n = 263)		D3 subgroup (n = 260)		
Factor	Multivariate odds ratio of BMI ≥ 25 (95% CI)	*P* value	Multivariate odds ratio of BMI ≥ 25 (95% CI)	*P* value	Interaction *P* value
Operation time					
Operation time > 297 min	2.19 (.96–5.02)	.063	2.27 (1.09–4.73)	.028	.95
Blood loss > 710 mL	2.83 (1.33–6.04)	.007	5.05 (2.27–11.26)	< .001	.30
Blood transfusion	1.73 (.70–4.26)	.23	0.78 (.34–1.79)	.56	.20
No. of retrieved lymph nodes ≤54	2.73 (1.28–5.85)	.01	1.06 (.43–2.62)	.9	.12
Reoperation	4.21 (.64–27.61)	.13	0.82 (.09–7.39)	.86	.27
Hospital death	6.82 (.40–117.43)	.19	NE	.98	.94
Any complication	2.62 (1.23–5.61)	.013	1.39 (.65–2.98)	.4	.25
Surgical complications	4.20 (1.59–11.10)	.004	2.60 (.91–7.40)	.074	.51
Anastomotic leak	2.77 (.47–16.19)	.26	1.49 (.16–14.09)	.73	.67
Pancreatic fistula	4.74 (1.42–15.89)	.012	3.61 (.96–13.55)	.057	.77
Abdominal abscess	4.72 (1.49–14.99)	.009	2.55 (.73–8.85)	.14	.48
Pneumonia	2.81 (.79–10.04)	.11	NE	.97	.94
Other complications	1.08 (.34–3.37)	.9	0.91 (.37–2.23)	.83	.82

Introduction Section- 1

- The incidence of overweight and obesity has been increasing in the general population, but the impact of increased BMI on surgical outcomes is unclear. Cancer surgery in overweight patients often takes longer, and is associated with greater blood loss than lean individuals due to the presence of excessive fat tissue impairing surgical procedures and lymph node dissection. The influence of increased BMI on the outcomes, e.g. surgical complications, surgical quality, hospital stay and prognosis, of gastrectomy with D2 lymph node dissection for gastric cancer patients is controversial.[1-5]

Introduction Section- 2

- These data were derived retrospectively from a single institution, but the surgical procedures and disease stages varied. A prospective study from multiple institutions using a similar surgical procedure is the ideal means to assess the impact of increased BMI on surgical outcomes and overall prognosis.
- A randomised trial, Japan Clinical Oncology Group (JCOG) 9501, was launched in 1995, to explore the potential survival benefit of extended para-aortic D3 dissection over standard D2 dissection. This trial provided the opportunity to prospectively evaluate collected data regarding the effect of increased BMI on surgical outcome following D2 or D3 dissection. Because a patient's physical condition including BMI could affect treatment indications for either D2 or D3, an observational study may not correctly compare potential differences between groups.

Introduction Section- 3

- Thus, we used the JCOG data to investigate the interaction of D2/D3 dissection and increased BMI on surgical complications in a randomized trial. In addition, we examined whether increased BMI directly influences the occurrence of complications or if the effects of increased BMI may be mediated by associated factors, such as operative time and blood loss.

Discussion Section- 1

- We clearly showed that overweight patients are at increased risk for the development of organ/space Surgical Site Infection (SSI) (abdominal abscess and pancreatic fistula) complications after gastrectomy with D2 or D3 dissection. Risk factors for the development of SSI in abdominal surgery have been intensively investigated… Among all of these studies, increased BMI was not identified as a risk factor for SSI… However, we analyzed operative time and blood loss as intermediate factors instead of outcome variables, and BMI was still associated with the development of pancreatic fistula and abdominal abscess as seen previously.[8] This fact suggests that BMI has a direct effect on surgical complications besides indirect effects through operative time or blood loss.

Discussion Section- 2

- Practically, the presence of a large amount of intraabdominal fat may disturb drainage of exudates and coagula, and excess fatty tissue may become necrotic more easily as a result of surgical manipulation. In addition, the demarcation between pancreas and fat tissues in overweight individuals is obscure because of greater fat deposition in the pancreas…[13,14] These factors may contribute to the increased occurrence of abdominal abscess and pancreatic fistula in surgical patients with increased BMI.

- The need for transfusion was not increased in patients with increased BMI, though the blood loss was significantly higher. Since criteria for preoperative hemoglobin value and blood transfusion were not defined in the protocol, this curious result could be observed by chance in the multi-institutional trial.

Discussion Section- 3

- Caucasians in general have a higher BMI than Japanese individuals, and the incidence of morbid obesity is significant and growing among patients in the USA and Europe. The proportions of patients with BMI≥25, BMI≥27 and BMI>30 in the present study were only 14.7%, 5.2% and 1.0%, respectively, whereas one-third of the US population is obese (BMI >27 kg/m2)…[15] The mortality of patients undergoing D2 dissection in the two Western studies was 13% and 10%, while morbidity was 46% and 43%. In contrast, we observed only 1.3% mortality and 35.1% morbidity in patients with BMI≥25 undergoing D2 or D3 dissection… In addition to possible differences in patients' physique, experience and workload volume of surgeons are important factors that could contribute to different surgical outcomes.

Discussion Section- 4

- In patients undergoing D2, but not D3, dissection, increased BMI was significantly associated with surgical complications. Although these differences were not statistically significant, this may be due to low statistical power to test the interactions. In contrast, only the odds ratios of long operative time and excessive blood loss increased were significant in the D3 dissection group, as reported previously.[6] The increased risk of complications in non-overweight patients in the D3 subgroup could explain these differences. Indeed, the cumulative incidence of all complications in non-overweight patients was 17.8% in the D2 subgroup and 27.6% in D3 subgroup. Thus, greater care should be taken in performing gastrectomy not only in all patients undergoing D3 dissection but also overweight patients undergoing D2 dissection.

Discussion Section- 5

- The relationship between increased BMI and overall prognosis in patients with cancer is an important issue to resolve. The presence of excess fat impairs precise nodal dissection and decreases the yield of lymph nodes. In this study, the number of lymph nodes retrieved from overweight patients was significantly less compared to non-overweight patients undergoing a D2, but not D3, dissection… The relationship between increased BMI and overall survival in gastric cancer patients remains controversial.[1-4] A conclusive result cannot be obtained without a well controlled prospective study, and the final results of the JCOG 9501 trial should answer this important question. However, the present study provides some insight into this issue.

Discussion Section- 6

- The proportion of overweight patients in this trial was low (14.7%). Therefore, the obtained results are not definitely conclusive, but clearly suggest that caution is needed when performing gastrectomy for gastric cancer in overweight patients.

- In conclusion, increased BMI increased the risk of surgical complications in patients undergoing gastrectomy with lymphadenectomy.

Decision Letter

ASO-2006-05-0290
Influence of overweight on surgical complications for gastric cancer: Results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501)

17-Jul-2006

Dear Dr. Tsujinaka:

The Editorial Board of the Annals of Surgical Oncology has reviewed your manuscript. I am pleased to inform you that they have accepted it for publication pending minor revision. The comments of the reviewer(s) are included at the bottom of this letter.

To submit your revised manuscript, log into https://mc.manuscriptcentral.com/aso and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number will be appended to denote a revision.

When submitting your revised manuscript, you will need to respond to the comments made by the reviewer(s) in the space provided. Please use this space to document any changes you have made to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

Take Home Messages

- 一流誌にアクセプトされるような、質の高い研究をしましょう
- どんどん英文を書いて、世界に情報発信しましょう
- レビューの依頼が来れば、どんなに忙しくても断らずに引き受けましょう