JCOG 0110　胃がん外科/SPNX

コピーして保管して下さい

a9609000109a

手術所見記録 2

術後14日以内にデータセンターに郵送

施設名　○○○○○がんセンター　　担当医　○× ○×

患者イニシャル　姓 A　名 A　　性別　男　　生年月日　昭和30年10月10日

カルテ番号　12345-6789　　割り付け群　＊ 群　　登録番号

記入者名：CRC記入可（自署）

西暦　　年　月　日

＜切除所見＞

1. 手術的根治度（胃癌取り扱い規約13版）　1□ 根治度A　2□ 根治度B　3□ 根治度C　99□ 不明

2. 脾臓摘出

A 群　0□ 温存　1□ 摘出 ↓

理由

B 群　0□ 温存　1□ 摘出 ↓

理由

3. 膵被膜剥離　0□ なし　1□ 一部　2□ 完全

4. 合併切除臓器　0□ なし　1□ あり →
□ 副脾　□ 副腎　□ 結腸　□ 胆嚢　□ 肝　□ 横隔膜
□ その他（　　）

5. 再建法　1□ R-en-Y　4□ 空腸間置　6□ ダブルトラクト　88□ その他（　　）

6. 切除近位断端（口側）　0□ PM（－）　1□ PM（＋）　99□ PMX

7. 切除遠位断端（肛門側）　0□ DM（－）　1□ DM（＋）　99□ DMX

8. 郭清リンパ節総個数　　個　（術当日に新鮮標本から摘出したリンパ節の総個数）

9. 各リンパ節郭清個数

No.10（脾門）	0□ 郭清せず	1□ 郭清 →	郭清個数	個
No.11p（脾動脈幹近位）	0□ 郭清せず	1□ 郭清 →	郭清個数	個
No.11d（脾動脈幹遠位）	0□ 郭清せず	1□ 郭清 →	郭清個数	個

備　考

DC記入

receive1(　)　check1(　)　check2(　)　input1(　)　input2(　)　confirm(　)

query(　)　receive2(　)　check3(　)　input3(　)　confirm(　)　fix(　)

(　)　(　)　(　)　(　)　memo

2002/02 JCOGデータセンター作成

JCOG 0110　胃がん外科/SPNX

コピーして保管して下さい

術後記録（術当日～初回退院）

退院後14日以内にデータセンターに郵送

施設名　○○○○○がんセンター　　担当医　○× ○×

患者イニシャル　姓：A　名：A　　性別　男　　生年月日　昭和30年10月10日

カルテ番号　12345-6789　　割り付け群　＊ 群　　登録番号

記入者名：CRC記入可（自署）

西暦　年　月　日

1. 術後合併症（手術当日～初回退院）

(1) 肺梗塞　0□ なし　1□ あり

(2) 腹腔内出血　0□ なし　1□ あり

(3) 縫合不全　0□ なし　1□ あり

(4) 膵液瘻　0□ なし　1□ あり

(5) 腹腔内膿瘍　0□ なし　1□ あり

(6) 吻合部狭窄　0□ なし　1□ あり → 内視鏡的ブジー　0□ なし　1□ あり

(7) イレウス　0□ なし　1□ あり → □ 麻痺性　□ 閉塞性

(8) 肺炎　0□ なし　1□ あり

(9) 深部静脈血栓症　0□ なし　1□ あり

(10) 術後4日以降の出血　0□ なし　1□ あり → ドレーンからの出血　0□ なし　1□ あり（出血量　ml）

(11) 術後人工呼吸器使用の有無　0□ なし　1□ あり

(12) その他の合併症　0□ なし　1□ あり

ありの場合

詳細

2. 手術翌日～初回退院の輸血

自己血　0□ なし　1□ あり → □□ 単位

全血　0□ なし　1□ あり → □□ 単位

濃赤　0□ なし　1□ あり → □□ 単位

3. 再手術

0□ なし　1□ あり → 再手術日 □□□□年 □□月 □□日

内容

4. 術後の初回退院日

□□□□年 □□月 □□日

0□ 軽快　2□ 転院による　1□ 死亡 →

詳細

コメント

DC記入						
receive1(　)	check1(　)	check2(　)	input1(　)	input2(　)	confirm(　)	
query(　)	receive2(　)	check3(　)	input3(　)	confirm(　)	fix(　)	
(　)	(　)	(　)	(　)	memo		

JCOG 0110　胃がん外科/SPNX

コピーして保管して下さい

9 606001 000110

病理所見記録 1

手術後病理所見が出たら速やかにデータセンターに郵送

施設名　○○○○○がんセンター　　担当医　○× ○×

患者イニシャル　姓 A　名 A　　性別　男　　生年月日　昭和30年10月10日

カルテ番号　12345-6789　　割り付け群　＊ 群　　登録番号

記入者名：CRC記入可(自署)

西暦　年　月　日

＜病理組織学的所見＞　胃癌取り扱い規約13版による

1. 最深部の組織学的深達度（T因子）　10□ pT1　20□ pT2　30□ pT3　40□ pT4　88□ その他(　)
   → 浸潤臓器 (　)
2. U領域の組織学的深達度（T因子）　10□ pT1　20□ pT2　30□ pT3　40□ pT4　88□ その他(　)
   → 浸潤臓器 (　)
3. 組織学的リンパ節転移（N因子）　00□ pN0　10□ pN1　20□ pN2　30□ pN3
4. 組織学的切除近位断端（口側）　0□ pPM(－)　1□ pPM(＋)　99□ pPMX
5. 組織学的切除遠位断端（肛門側）　0□ pDM(－)　1□ pDM(＋)　99□ pDMX
6. 原発巣の主な組織型(1つ選択)　10□ 乳頭腺癌(pap)　21□ 管状腺癌－高分化型(tub1)　22□ 管状腺癌－中分化型(tub2)　31□ 低分化腺癌－充実型(por1)　32□ 低分化腺癌－非充実型(por2)　40□ 印環細胞癌(sig)　50□ 粘液癌(muc)　88□ その他(　)
7. 総合的根治度　1□ fA　2□ fB　3□ fC
8. 総合Stage　11□ ⅠA　12□ ⅠB　20□ Ⅱ　31□ ⅢA　32□ ⅢB　40□ Ⅳ

各リンパ節の転移の有無

		転移個数		郭清個数	
1 右噴門	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
2 左噴門	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
3 小彎	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
4sa 大彎左群(短胃動脈)	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
4sb 大彎左群(左胃大網動脈に沿う)	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
4d 大彎右群(右胃大網動脈に沿う)	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
5 幽門上	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
6 幽門下	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
7 左胃動脈幹	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明
8a 総肝動脈幹前上部	0□ 郭清せず　1□ 郭清 →	個	99□ 不明	個	99□ 不明

コメント

DC記入　receive1(　) check1(　) check2(　) input1(　) input2(　) confirm(　)
query(　) receive2(　) check3(　) input3(　) confirm(　) fix(　)
(　) (　) (　) (　) (　) memo

JCOG 0110　胃がん外科/SPNX

コピーして保管して下さい

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病理所見記録 2

手術後病理所見が出たら速やかにデータセンターに郵送

施設名　○○○○○がんセンター　　担当医　○× ○×

患者イニシャル　姓 A　名 A　　性別　男　　生年月日　昭和30年10月10日

カルテ番号　12345-6789　　割り付け群　＊ 群　　登録番号

記入者名：CRC記入可(自署)

西暦　年　月　日

			転移個数		郭清個数	
8p 総肝動脈幹後部	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
9 腹腔動脈周囲	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
10 脾門	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
11p 脾動脈幹近位	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
11d 脾動脈幹遠位	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
12a 肝十二指腸間膜内(肝動脈に沿う)	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
12b 肝十二指腸間膜内(胆管に沿う)	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
12p 肝十二指腸間膜内(門脈に沿う)	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
13 膵頭後部	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
14a 上腸間膜動脈に沿う	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
14v 上腸間膜静脈に沿う	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
15 中結腸動脈周囲	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
16a1 腹部大動脈周囲a1	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
16a2 腹部大動脈周囲a2	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
16b1 腹部大動脈周囲b1	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
16b2 腹部大動脈周囲b2	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
17 膵頭前部	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
18 下膵	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
19 横隔下	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
20 食道裂孔部	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
110 胸部下部傍食道	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
111 横隔上	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明
112 後縦隔	0□ 郭清せず	1□ 郭清 →	個	99□ 不明	個	99□ 不明

リンパ節郭清総個数　　個

リンパ節転移個数　　個

コメント

DC記入						
receive1( )	check1( )	check2( )	input1( )	input2( )	confirm( )	
query( )	receive2( )	check3( )	input3( )	confirm( )	fix( )	
( )	( )	( )	( )	memo		

2002/02 JCOGデータセンター作成

JCOG 0110　胃がん外科/SPNX　　調査

追跡調査用紙

までにデータセンターに郵送

施設名　　担当医

患者イニシャル　姓　名　性別　生年月日

カルテ番号　　登録番号

記入者名：CRC記入可（自署）

西暦　年　月　日

遅発性合併症
（有害反応）

・「肺炎」「感染」はプロトコール治療との因果関係が否定できないもの（ definit, probable, possible ）で、イベントの回数を記入（イベントなしは「0」と記入）

・「リンパ球数」と「アルブミン」の検査日は同一日であること

＊38℃以上の発熱を伴うその他の感染

項目＼術後	3ヶ月	6ヶ月	9ヶ月	1年	1.5年	2年	2.5年	3年	3.5年	4年	4.5年	5年
肺炎	回	回	回	回	回	回	回	回	回	回	回	回
感染＊	回	回	回	回	回	回	回	回	回	回	回	回
体重	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg	kg
リンパ球数	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日	/mm³ 月 日
アルブミン	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日	g/dl 月 日

再発の有無　0□ 再発なし　1□ 再発あり　0□ 不明

無再発または不明の場合　最終無再発生存確認日　西暦　年　月　日

再発の場合　初再発判定日　西暦　年　月　日

前回調査の報告

初再発部位　□リンパ節（部位　）　□肝　□ 腹膜転移　□ 遠隔転移（　）　□その他（　）

再発状況

後治療　0□ なし　1□ 後治療あり

□ S-1　投与開始日 西暦　年　月　日 ～ 投与終了日 西暦　年　月　日　total　コース

□ その他（　）

転帰　0□ 生存　最終生存確認日　西暦　年　月　日

前回調査の報告　1□ 死亡　死亡日　西暦　年　月　日

死因　1□ 原病死　2□ 他病死　3□ 治療関連死　8□ その他　9□ 不明

死亡の状況

いずれの死因の場合も死亡時の状況を記入

コメント

DC記入

receive1(　) check1(　) check2(　) input1(　) input2(　) confirm(　)

query(　) receive2(　) check3(　) input3(　) confirm(　) fix(　)

(　) (　) (　) (　) memo

説明同意文書

研究名：JCOG 0110-MF ver2.1「上部進行胃癌に対する胃全摘術における脾合併切除の意義に関するランダム化比較試験」

1) あなたの病状

担当医から説明がありましたように、あなたの胃にがんができています。あなたの胃がんは進行がんと考えられており、胃の入り口に近い部位に生じていて、完全に切除するためには胃を全部摘出すること（胃全摘）が必要です。ただし肝臓や遠くのリンパ節への転移は見つかっておらず、手術で根治が望める状態であると考えられています。胃がん手術後の予後は、がんの深さ、リンパ節転移の程度、腹膜や肝臓などへの転移の有無によって決まります。胃がんの進行程度を表すステージ（病期）は、ステージ 1A、1B、2、3A、3B、4 の 6 段階ありますが、これまでの検査の結果、あなたの胃がんはステージ 1B から 4 までの範囲にあると考えられ、予想される 5 年生存率も 20%から 90%と幅があります。最終的なステージは手術後の病理検索の結果で決まります。

2) 胃がんとリンパ節転移、リンパ節郭清、予後

胃がんはリンパ節に転移しやすいがんです。リンパ節転移が進むと、全身にがん細胞が広がります。早期胃がんでも約 10%、進行がんでは 50%以上の確率でリンパ節転移が認められます。胃がんのリンパ節転移は、胃のすぐそばのリンパ節（第 1 群リンパ節）に生じて徐々に離れた部位（第 2 群、3 群リンパ節）へと広がりますので、たとえ転移があってもこれを遠くから包み込むようにして十分に切除することにより、治癒する可能性が得られます。リンパ節に転移があるかどうかは手術中には正確に判断できず、摘出したリンパ節を術後に顕微鏡で検査して初めて転移の有無が判明します。リンパ節の切除（郭清（かくせい）といいます）は、胃がんの手術において重要な部分を占めており、通常、第 2 群までのリンパ節が郭清されます。

3) 上部胃がんと脾臓

胃がんでは、がんが胃のどの位置にあるかによって、転移しやすいリンパ節の場所が変わります。「第 2 群リンパ節」といっても、胃の上部のがんと下部のがんでは範囲が異なるのです。胃の左背側には脾臓という握りこぶしくらいの大きさの臓器がありますが、胃上部のがんの場合、この脾臓のすぐそば（脾門部）のリンパ節にも転移することがあり、この脾門リンパ節も第 2 群に含まれています。したがって、胃上部の進行胃がんに対しては、胃と同時に脾臓も合併切除することが行われてきています。

4) 脾臓の役割

脾臓は、古くなった血小板などの血液成分を壊す働きがあります。また、体の免疫の調整に関しても一役を担っています。脾臓を摘出（脾摘）すると、一時的に血液中の血小板の数が増加しますが、やがて骨髄が代役を果たすようになりますので数ヶ月で血小板数は元に戻ります。また、免疫力が低下することがあり、肺炎球菌などの感染が起こりやすく

なるとされています。脾臓はまた、腫瘍に対する生体の免疫に関与するという研究がありますが、脾臓を摘出することが腫瘍の増殖とどう関係するかは、明確にされていません。

5)　胃全摘と脾摘

胃上部の進行がんでは胃全摘とともに脾摘も行われると述べましたが、実は脾臓を同時に摘出することの意義はきちんと証明されているわけではありません。脾門部のリンパ節に転移があった場合、脾摘を行うとこの転移を切除することができますが、一方で、脾摘操作により術中の出血量が増え、術後の合併症（脾臓のそばにある膵臓からの膵液の漏れや、腹腔内の感染）が生じやすくなったり、脾臓を失うことにより体の免疫力が低下して肺炎球菌という細菌の感染症が増えたりする可能性もあります。西洋諸国では、脾摘により術後の合併症率や手術死亡率が明らかに高くなるため、近年これを極力避けようという考えが支配的になっています。しかしわが国では、術後合併症は増えても手術死亡率が高くなるという事実はなく、むしろ転移リンパ節を切除する意義が注目されています。

これまでに胃上部進行がんで脾摘を行った記録を検討すると、約15～20%の患者さんで脾門リンパ節に転移が見られ、その転移のある患者さんの20～25%が5年以上生存しています。つまり脾摘をしたから助かった、と考えられる患者さんがいます。ところが一方、脾摘をした患者さん全体としなかった患者さん全体を比べると、脾摘をしなかった患者さんの生存率の方が高いという結果も出ています。ただしこれは、より進行したがんの場合ほど脾摘が行われることが多いため、脾摘患者さんの生存率が低く出てしまうとも解釈されています。

6)　この臨床試験について

このように、胃上部の進行がんに対して胃全摘を行う場合に、同時に脾摘を行うことが生存の可能性を高めるかどうかは分かっていません。これまでにも多くの学会で論じられてきましたが結論は出ていません。

この問題に科学的な結論を下すためには、きちんと計画された臨床試験が必須となります。本臨床試験は、がんの専門病院を中心に構成される日本臨床腫瘍研究グループ（JCOG）の胃がん外科チームが厚生労働省の研究費を得て計画したもので、同じような病態の多数の患者さんに、脾摘を行うグループと行わないグループに分かれていただき、長期間経過を追って、どちらが優れた術式かを決めようというものです。この臨床試験で得られた結果は、将来、多くの胃がん患者さんが胃全摘を受ける際に、脾摘が行われるかどうかを決定する大変重要な根拠となるはずです。

7)　この臨床試験の実際の手順

あなたがこの臨床試験への参加に同意されたとしましょう。手術が始まり、通常の手順で腹腔内が検索されます。腹膜転移や肝転移がないことが確認され、腹膜洗浄細胞診も行われます。大動脈周囲などの胃から離れた部位のリンパ節に転移がないこと、さらに脾門部にも明らかに腫脹したリンパ節はないことが確認されます。胃全摘を行えばがんは取り切れそうだ、という段階にきました。ここまで確認して初めて、臨床試験に登録するかど

うか決定されます。以上のうちどれか一つでも当てはまらない場合は、臨床試験には入らずに、担当医が最良と考える治療が行われます。

臨床試験に登録されると、胃全摘に加えて脾摘を行うかどうかが決定されることになります。二つのグループで患者さんの特徴に偏りが生じないよう、病院とは独立した JCOG のデータセンターが、ランダム割付けと呼ばれる方法で決定します。この結果にしたがって手術が行われます。あなたは手術後に、担当医から脾摘が行われたかどうかを知らされますが、その後の治療や経過観察は脾摘の有無にかかわらずまったく同じように行われます。この臨床試験には、合計 500 人の患者さんの登録を予定しています。

進行胃がんの手術後に、再発を予防する目的で抗がん剤が使われることがあります。これまでの多くの臨床試験では、手術でがんが取りきれたと考えられる場合に抗がん剤を使うこと（補助化学療法といいます）により再発の危険性を減らすことができるという結論は得られていませんでしたので、本臨床試験でも補助化学療法を行わずに経過を観察することにしていました。しかし 2007 年 1 月に、1000 人以上の進行胃がんの患者さんが参加された大規模な臨床試験において、S-1 という抗がん剤を手術後に服用すると生存期間が延長するという結果が報告されたため、それ以降は進行胃がんの手術後に S-1 を 1 年間服用することが標準治療であると考えられるようになりました。したがって、本臨床試験でも 2007 年 6 月に研究計画を一部改訂し、以降に参加していただく患者さんについては手術後のステージが 2 から 3B までの間に入っていた場合は、原則として S-1 を 1 年間服用していただくことになりました。もちろん不幸にも再発が判明した場合にも、抗がん剤による化学療法を中心に最善の対処をいたします。

8)　その他の治療法について

あなたの胃がんを治療するには、内視鏡的切除では不十分で、手術が必要です。また、抗がん剤や放射線療法だけでは治癒は望めません。手術方法としては、ご説明しました胃全摘術の他に、胃の下部を残す噴門側胃切除術という方法があります。ただし、あなたの胃がんでは十分な範囲の胃とリンパ節を切除する必要があるため、たとえ胃の下部を残しても十分な機能は望めず、むしろ食べ物の流れが悪くなる場合もありますので、胃全摘が望ましいと考えられています。リンパ節の郭清範囲では、ご説明しました第 2 群までの郭清が現在標準的に行われていますが、さらに遠くの第 3 群までの郭清も技術的には可能です。ただし第 3 群までの郭清が胃がんの治癒に貢献するかどうかは分かっておらず、現在臨床試験が進められています。

9)　この臨床試験に参加することの利益と不利益

この臨床試験に参加することで、医療費の免除などの直接的な利益は得られません。もちろん従来から行われている手術ですので、経済的負担が増えるということもありません。

臨床試験に登録されるかどうかは、手術中に腹腔内を十分検索してから決定されますので、この試験に同意したからといって無理やり無用な手術が行われるということもありません。脾摘を行うことも行わないことも、外科医には十分に慣れた手順ですから、新しい

種類の合併症が生じるということもありません。

この臨床試験では術後 5 年間にわたる経過追跡の内容が詳細に規定されていますので、試験に参加しない場合よりも細かいフォローアップが行われることになるでしょう（そのために若干医療費が増える可能性があります）。

10) この臨床試験への参加に同意されなかった場合、および同意の撤回

この臨床試験への参加に同意されなかった場合でも、あなたはいかなる不利益も受けることはありません。また一旦同意しても、いつでもこれを撤回することができます。

11) 人権およびプライバシーの保護、データの二次利用

この臨床試験に参加した場合、あなたのお名前や個人情報は厳重に保護されます。データセンターのデータベースにも、あなたのお名前は登録されません。

この試験が適正かつ安全に実施され、患者さんの人権が守られており、かつ検査や診断の結果が正しく報告されていることを確認する目的で、JCOG 委員会の指名する他の医療機関や研究機関の研究者（医師など）が、あなたのカルテや検査記録を直接見にくる調査を行うことがあります。この場合もあなたの個人的情報は厳重に守られ、外部に漏れることはありません。

また、JCOG 委員会が承認した場合に限り、あなたの個人識別情報とリンクしない形でデータを二次利用する可能性があります（本臨床試験と同様の目的で行われた他の試験と、総合的に解析する場合、など）。この場合もあなたの個人的情報は厳重に守られます。

12) 質問の自由

この臨床試験の内容や治療の内容について、ご不明な点がありましたらご質問ください。

この臨床試験の当院における研究責任者、担当医は、

です。

この臨床試験の研究代表者および研究事務局は以下の通りです。

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同 意 書

＿＿＿＿＿＿＿＿＿＿＿＿病院長　殿

カルテ番号　＿＿＿＿＿＿＿＿

患者氏名　＿＿＿＿＿＿＿＿

臨床研究名：JCOG 0110-MF ver 2.1「上部進行胃癌に対する胃全摘術における脾合併切除の意義に関するランダム化比較試験」

説明内容：

- ☐ 病名、病状、予後
- ☐ 本研究が臨床試験であること。厚生省研究助成金に基づく公的研究であること。
- ☐ 試験の背景、目的、意義
- ☐ 治療の内容
- ☐ 治療法がランダム割付されること
- ☐ 治療により期待される効果と予測される副作用
- ☐ 費用が保険制度に従った自己負担であること
- ☐ 本試験に参加しなかった場合に受けられる他の治療法
- ☐ 試験参加に伴って生じる利益と不利益
- ☐ 試験に参加しない場合でも不利益を受けないこと
- ☐ 試験への参加に同意した後でも随時これを撤回できること
- ☐ 第三者による病歴の直接閲覧の可能性、データ二次利用の可能性
- ☐ プライバシーは守られること
- ☐ 現状に応じた変更の可能性（緊急の場合等の医学的処置）
- ☐ 質問の自由

上記の臨床試験について、担当医から説明を受けよく理解しましたので、試験に参加します。

患者本人署名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

署名年月日　：　平成　　年　　月　　日

私は、今回の試験について上記の項目を説明し、同意が得られたことを認めます。

担当医署名　：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

説明年月日　：　平成　　年　　月　　日

署名年月日　：　平成　　年　　月　　日

Adjuvant and Neoadjuvant Therapy of Gastric Cancer: A Comparison of Three Pivotal Studies

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In the past, the role of adjuvant therapy for gastric cancer was indefinite. However, three large, randomized controlled trials have recently shown the survival benefit of adjuvant therapy over surgery alone: the American INT 0116 trial, with adjuvant chemoradiation therapy; the European MAGIC trial, with perioperative combination chemotherapy; and the Japanese ACTS-GC trial, with adjuvant monotherapy. Because the patient populations and surgical approaches are considerably different among these trials, it is not sensible to simply compare survival rates to determine the best modality. In the time since these pivotal trials, various innovative studies have been planned and launched to evaluate treatment factors including modality (chemotherapy or chemoradiation), timing (before and/or after surgery), and different surgical extent (D1 or D2 lymphadenectomy). Because the East and West have different backgrounds and treatments for localized gastric cancer, each region should design its own clinical trial to determine the best evidence-based treatment regimens.

Introduction

Adjuvant therapy aims to improve survival by eliminating residual micrometastatic disease after curative resection of solid tumors. Gastric cancer has long been a focus of adjuvant studies; however, numerous past trials failed to prove the benefit of adjuvant therapy. Although some meta-analyses showed statistically significant superiority of adjuvant chemotherapy, they could not provide clinically significant conclusions due to the heterogeneity in therapeutic regimens, disease stages, and quality of surgery among the studied trials [1,2]; all phase 3 trials thus needed a control arm of surgery alone to produce evidence. The absence of a pivotal trial in adjuvant therapy for gastric cancer could be attributed to two reasons: 1) the absence of powerful treatment regimens to improve survival, and 2) the difficulty in conducting a large-scale, randomized controlled trial with sufficient statistical power for this disease.

Recently, three different modalities of adjuvant therapy for localized gastric cancer were proven to improve survival in three large-scale, randomized controlled trials conducted in three different regions in the world. These trials, the SWOG 9008/INT 0116 trial (INT 0116) of adjuvant chemoradiation in the United States [3], the MAGIC trial of perioperative three-agent chemotherapy in Europe [4••], and the ACTS-GC trial of adjuvant S-1 monotherapy in Japan [5••] have led to a new phase in this field of study.

Because these studies have different patient populations and surgical approaches, cross-trial comparisons of the survival results are not easy. In this review, these trials are carefully compared with special reference to the patient selection and the role of surgery. Currently active clinical trials and future directions are also discussed.

Overview of the Three Trials

The INT 0116 trial

The eligibility criteria for the INT 0116 study included stage IB through IV M0 adenocarcinoma of the stomach or gastroesophageal junction, with registration occurring 20 to 41 days after complete resection with free resection-line involvement. Of the 603 patients registered between 1991 and 1998, 556 were eligible and randomly assigned to surgery only (n = 275) or to surgery plus chemoradiotherapy (n = 281). The adjuvant regimen consisted of 5-fluorouracil (5-FU) (425 mg/m^2) plus leucovorin (20 mg/m^2) for 5 days, followed by a total of 45-Gy radiation given for 5 weeks with modified doses of 5-FU/leucovorin, and two 5-day cycles of 5-FU (425 mg/m^2) plus leucovorin (20 mg/m^2). Chemoradiotherapy was completed as planned in 64% of patients; it was stopped in 25% because of toxic effects or patient declination. Three patients (1%) died of toxic effects.

More than half the tumors were located in the antrum, and about 20% were in the cardia. Sixty-nine percent of the tumors were T3 or T4, and 85% had nodal metastases. The review of the surgical records of 552 patients showed that, although the study protocol had recommended D2 lymphadenectomy, the majority underwent limited resection (54% D0, 36% D1, 10% D2). With a median follow-up of 5 years, the median survival time and the 3-year survival rates of the surgery and surgery-plus-chemoradiation groups were 27 months (41%) and 36 months (50%), respectively. The first site of recurrence was more local-regional in the surgery-only group than in the adjuvant group.

The MAGIC trial

The eligibility criteria for the MAGIC trial included stage II or higher M0 adenocarcinoma of the stomach or lower third of the esophagus that was deemed resectable. Between 1994 and 2002, 503 patients were randomly assigned to surgery alone (n = 253) or to perioperative chemotherapy and surgery (n = 250). The chemotherapy consisted of three preoperative and three postoperative cycles of ECF: epirubicin (50 mg/m^2) plus cisplatin (60 mg/m^2) on day 1 and a continuous intravenous infusion of 5-FU (200 mg/m^2) for 21 days. Of the 237 patients who started preoperative chemotherapy, 215 (90.7%) completed it, and 209 of this subset proceeded to surgery. Postoperative chemotherapy was started in 137 patients and was completed in 104 patients (41.6% of the chemotherapy group).

Surgery was performed in 91.6% of the chemotherapy group and in 96.4% of the surgery group. Resection was curative in 69.3% of the chemotherapy group and 66.4% of the surgery group. The extent of lymphadenectomy was not specified in the protocol and was decided by the surgeon. The postoperative mortality rates were similar between the two groups (5.6% and 5.9%). In the surgery group, 63.2% of tumors were T3 or T4, and 73.1% had lymph node metastases. In the chemotherapy group, the tumor diameter was smaller, the proportion of T1 and T2 was greater, and the proportion of N0 and N1 was greater than in the surgery group, suggesting the downstaging effect of preoperative chemotherapy.

With a median follow-up of 47 to 49 months, the overall and progression-free survival rates in the chemotherapy group were significantly better than those in the surgery group. The 5-year survival rates were 36.3% in the chemotherapy group and 23.0% in the surgery group. Both local and distant recurrences were more frequently seen in the surgery group.

The ACTS-GC trial

The eligibility criteria for the ACTS-GC trial included stage II (excluding T1), IIIA, or IIIB adenocarcinoma of the stomach, after D2 or more extensive curative surgery, with no tumor cells in the peritoneal lavage cytology; patients were also no older than 80 years of age. Between 2001 and 2004, 1059 patients were registered from 109 high-volume hospitals in Japan and were randomly assigned to surgery only (n = 530) or to adjuvant chemotherapy (n = 529). The chemotherapy consisted of 6-week cycles of S-1 (an orally active fluoropyrimidine [6–8]; 80 mg/m^2 for 4 weeks followed by 2-week rest) for 1 year starting within 6 weeks postoperatively. This regimen was continued for at least 3 months in 87.4% of patients, for 6 months in 70.8%, and for 12 months in 65.8%. Dose modification due to toxicity was necessary in 42.4% of patients. The tumors were predominantly located in the distal stomach; 58% were treated by distal gastrectomy. Forty-six percent of the tumors were T3 or T4, and 89% had lymph node metastasis.

The study was designed to compare the 5-year overall survival, but the first interim analysis with a median follow-up of 2 years showed a significant difference in overall and relapse-free survival in favor of the chemotherapy group, and the trial was discontinued. In the published data, with a median follow-up of 2.9 years, the 3-year overall survival rates were 80.1% in the chemotherapy group and 70.1% in the surgery group. Fewer relapses in peritoneum and lymph nodes were observed in the chemotherapy group. Subgroup analyses showed no interaction between any studied variables.

Comparison of the Three Trials

Patient population

Curability

The patient population was essentially different between the MAGIC trial and the other two trials. MAGIC recruited cases deemed to be resectable, whereas the other two studies included only patients after curative gastrectomy. It has been well established that R0 resection without gross or microscopic residual disease is one of the most important prognostic determinants of gastric cancer [9,10].

Curability of gastric cancer without apparent distant metastasis largely depends on peritoneal dissemination. Staging laparoscopy with biopsy is the only method available to diagnose this before definitive surgery. In the MAGIC trial, laparoscopy was listed as a staging method but did not seem to have been employed in many patients: in 28% of the patients assigned to the surgery group, the operation turned out to be noncurative at laparotomy, and half of these individuals underwent nonresectional surgery.

Contamination of noncurative cases is inevitable in neoadjuvant trials but should be avoided with every effort. It is especially important to exclude individuals with peritoneal metastasis that is most refractory to chemotherapy. In current ongoing trials for neoadjuvant therapy, staging laparoscopy is usually mandatory to exclude peritoneal disease and is useful to select patients who may truly benefit from the treatment [11•].

Tumor stage

In the INT 0116 and ACTS-GC trials, only patients with pathologically confirmed stages after curative resection were recruited. More T3/T4 tumors were included in INT 0116 (69%) than in ACTS-GC (46%), but lymph node metastasis was less frequently detected in INT 0116 (85%) than in ACTS-GC (89%). It is well established that incidence and extent of nodal metastasis closely correlate with T stage of the primary tumor [12]; therefore, the above observation may appear contradictory. This may be explained by the fact that lymphadenectomy and postoperative nodal retrieval are more extensively performed in Japan; thus, small nodal disease possibly overlooked in the US trial could be detected.

In the MAGIC trial, it is difficult to determine the exact proportions of T and N stages of gastric cancer from the published data, partly because they were presented together with esophageal cancers and partly because there are several missing or "unknown" data. Nodal status is available in 156 of 187 gastric cancer patients in the surgery group, and only 114 (73%) had nodal metastasis, which is considerably lower than the other two trials (85% for INT 0116 and 89% for ACTS-GC). However, this is likely to be an underestimation because nonresectable cases with high probability of nodal metastasis were not included in this calculation.

A notable eligibility criterion used in ACTS-GC was the negative result of peritoneal cytology. Free cancer cells detected in the lavage fluid at the beginning of laparotomy or staging laparoscopy are a strong indicator of poor prognosis [13•], and the Japanese Classification [14] includes this as a determinant of the disease stage (ie, a tumor with positive cytology is staged as IV regardless of the T or N status). Exclusion of patients with positive cytology facilitates selection of patients with minimal residual disease who thus may benefit from adjuvant chemotherapy.

In all, Japanese patients in ACTS-GC were a highly selective population with the best prognosis among the three trials. Patients in MAGIC had the poorest prognosis at the time of registration because a considerable proportion had noncurative, even unresectable, disease. American patients in INT 0116 had more advanced T3/T4 disease than the Japanese patients but with better prognosis than the MAGIC population because they had undergone at least grossly curative resection.

Tumor site and type of surgery

Today, there is a remarkable difference between the East and the West in regard to the anatomical location of gastric cancer; in the West, a prominent shift to the proximal stomach exists [15,16]. Nevertheless, most tumors in the INT 0116 trial were located in the distal stomach, and 60% of the patients underwent distal gastrectomy. It is interesting that this rate of distal gastrectomy was very similar to that in the Japanese ACTS-GC trial (58%).

The MAGIC trial initially recruited only patients with gastric cancer, but extended the inclusion criteria to those with adenocarcinoma of the lower esophagus in the last 3 of the 8 accrual years. Fourteen percent of the tumors in the trial were lower esophageal cancer, and 22% of the patients in the surgery group underwent esophagogastrectomy. Of the other 146 gastric resections in this group, distal gastrectomy accounted only for 37%, indicating the predominance of proximal tumors in the trial.

The predominance of distal tumors in ACTS-GC and that of proximal tumors in MAGIC appears to reflect the general background of the disease in each region, although the patients in the INT 0116 trial may not represent American gastric cancer patients. The strict eligibility criteria of curative gastrectomy may have excluded many proximal or esophagogastric junction tumors which are, in general, locally more aggressive than distal tumors [17].

Lymphadenectomy

In adjuvant trials, surgery does not draw much attention because it is not a tested variable; rather it is a constant that is supposed to be the same or alike between the compared arms. However, when the results of separate studies are compared or combined for meta-analysis, the quality of surgery should be considered with great attention. In most solid tumors, including gastric cancer, surgery still plays the key role for cure, and the extent of surgery can easily alter the volume of residual tumor burden. If an adjuvant therapy aims at the systemically scattered cancer cells, the difference of surgery does not much matter. However, if the local residual disease is an important prognostic determinant to be targeted by adjuvant therapy, as in INT 0116, extent of surgery should be strictly controlled because it will directly affect the trial end points.

In the ACTS-GC trial, great attention was given to the quality assurance of surgery. Only high-volume centers participated in the study, the extent of lymphadenectomy was carefully reviewed, and the minimum requirement of D2 was confirmed before registration. In a D2 lymphadenectomy, the perigastric (N1) nodes and those along the branches of the celiac artery (N2) are completely removed [14].

In the INT 0116 trial, the operative records were reviewed in terms of lymphadenectomy, and it was found that the vast majority (90%) of patients had undergone limited lymphadenectomy [18]. Considering the high incidence of pathological nodal involvement in these patients (85%), microscopic disease must have remained in the nodes around the celiac artery in a considerable proportion of cases. In the subset analysis of the long-term results, chemoradiation did not improve survival of patients undergoing D2 lymphadenectomy [19]. Thus, the positive results of this study could be interpreted to mean that chemoradiation therapy was effective in eradicating the residual local disease, thereby reducing local recurrence and subsequent systemic metastasis.

Table 1. Survival data of three pivotal trials

	INT 0116	MAGIC*	ACTS-GC
Surgery group			
3-year overall survival, %	41	31	70.1
3-year relapse-free survival, %	31	25	59.6
Chemo(radiation) group			
3-year overall survival, %	50	44	80.1
3-year relapse-free survival, %	48	40	72.2
Hazard ratios between arms			
Death	0.74	0.75	0.68
Progression	0.66	0.66	0.62

*Three-year survival rates in MAGIC trial were not shown (Cunningham et al. [4••]). The listed figures were estimations obtained from the survival curves presented.

In the MAGIC trial, the extent of lymphadenectomy was at the surgeon's discretion. Cunningham et al. [4••] reported that D2 lymphadenectomy was performed more frequently than D1 (96 and 50 cases, respectively, in the surgery group); however, this cannot be accepted at face value. First, these terms were used inaccurately (the researchers incorrectly termed "D1" as denoting limited lymph node dissection, and "D2" as denoting extended lymph node dissection), suggesting that a precise review of operative records, such as in the INT 0116 study, did not occur. Second, D2 lymphadenectomy, in its properly defined context, was not the standard of surgery in Europe at the time of the trial. Extremely high hospital mortality rates following D2 lymphadenectomy in both the Dutch D1/D2 trial and the British D1/D2 trial (10% and 13%, respectively) had been recently published (1995 and 1996) [20,21] at the time of MAGIC trial accrual (between 1994 and 2002); therefore, surgeons participating in the MAGIC trial had no strong reason to perform this dangerous surgery, especially after intensive chemotherapy. Indeed, the operative mortality of the MAGIC trial (5.4% in the chemotherapy group and 5.9% in the surgery group) was even lower than that of D1 group in the British D1/D2 trial (6.5%). Therefore, it seems inappropriate to consider that the surgery was more radical in MAGIC than in INT 0116 [22].

Survival

The survival data of the three trials are summarized in Table 1. Following publication of the INT 0116 and MAGIC trial data, many discussions have arisen regarding which therapy—adjuvant or perioperative—is superior in terms of survival [23]. However, this comparison requires special attention because these trials had essentially different populations in terms of curability and disease stages, as discussed above. Despite the difference in the survival rates between the two trials, the hazard ratios for both death and progression between the surgery and treatment arms were exactly the same.

There was a strikingly large difference in baseline survival between the Japanese study and the other two trials. The 3-year overall and relapse-free survival rates in the surgery group of ACTS-GC were almost twice as high as those in INT 0116 and MAGIC. Again, this should be attributed to the population differences discussed above. A more aggressive surgical approach in Japan may also have contributed to this survival difference. However, the 3-year survival of gastrectomy plus chemoradiation in INT 0116 (50%), which could be considered a result of optimal local therapy, was still far inferior to that of the Japanese surgery-only group (70.1%); the difference in local control alone cannot explain such a large survival difference.

Other Recently Concluded and Currently Ongoing Studies

In the time since the three pivotal studies discussed previously, other clinical studies in the United States, Europe, and East Asia have recently concluded or are ongoing (Table 2).

Studies in the United States

Following INT 0116, adjuvant chemoradiotherapy has become a standard treatment option in the United States; all ongoing clinical trials for localized gastric cancer now include chemoradiation. In a phase 3 trial (CALGB-80101), the chemoradiation regimen used in the INT 0116 trial is being compared with one in which the ECF regimen of the MAGIC trial is used rather than 5-FU/leucovorin [24].

Neoadjuvant chemoradiation is a new subject drawing great attention. A phase 2 trial (RTOG 9904) in a cooperative study setting tested a regimen consisting of 5-FU/leucovorin/cisplatin induction followed by concurrent 45-Gy radiation and 5-FU, as well as weekly paclitaxel prior to surgical resection. Results showed pathological complete response in 26% and favorable survival of responders [11•]. Other chemotherapeutic regimens currently being evaluated in combination with radiation include capecitabine and oxaliplatin (SWOG-S0425) [25].

Table 2. Currently active phase 3 trials on (neo)adjuvant therapy for gastric cancer

Study	Country	Patients, *n*	Disease	Therapeutic modes
CALGB-80101 [24]	USA	824	Stage Ib–IV M0	Surgery + chemoradiation (RT + 5-FU/leucovorin) vs surgery + chemoradiation (ECF)
MRC-ST03 [29]	United Kingdom	1100	Stage Ib–IV M0	ECX + surgery + ECX vs ECX/bevacizumab + surgery + ECX/bevacizumab + bevacizumab
CRITICS [30]	The Netherlands	788	Stage Ib–IVa M0	ECC + surgery + ECC vs ECC + surgery + chemoradiation (RT + capecitabine/cisplatin)
CLASSIC [31]	Korea	1024	Stage II, III	Surgery vs surgery + capecitabine/oxaliplatin
SMC IRB [33]	Korea	490	Stage Ib–IV M0	Surgery + capecitabine/cisplatin vs surgery + chemoradiation (RT + capecitabine/cisplatin)
SAMIT [34•]	Japan	1480	T3–4, N0–2	Surgery + UFT vs surgery + S-1 vs surgery + paclitaxel + UFT vs surgery + paclitaxel + S-1
JCOG 501 [36]	Japan	316	Linitis plastica/large ulcerative tumor	Surgery + S-1 vs S-1/cisplatin + surgery + S-1

The ECC and ECX regimens comprise the same chemotherapy elements; however, because different trials use these agents in different doses or timings, the abbreviations have been set to match the original expressions used in the respective citation and/or trial registration.
5-FU—fluorouracil; ECC/ECX—epirubicin, cisplatin, capecitabine; ECF—epirubicin, cisplatin, 5-FU; RT—radiation therapy; UFT—tegafur–uracil.

Studies in Europe

The results of a French neoadjuvant randomized controlled trial were presented at the American Society of Clinical Oncology meeting in 2007 [26]. A total of 224 patients with adenocarcinoma of the lower esophagus (11%), esophagogastric junction (64%), or stomach (25%) were enrolled between 1995 and 2003. The chemotherapy group received two to three courses of 5-FU/cisplatin before surgery, whereas the surgery group immediately proceeded to surgery without additional chemotherapy. The responders of the neoadjuvant group also received postoperative chemotherapy. The 5-year overall survival rate was 38% in the chemotherapy group and 24% in the surgery group (HR 0.69; $P = 0.02$). Although the publication of the details is awaited, this can be considered supportive evidence for the MAGIC trial.

The ECF regimen is now undergoing modifications, as the UK National Cancer Research Institute REAL-2 study for advanced disease showed noninferiority of oral capecitabine to infusional 5-FU [27]. In the "MAGIC-B" trial (MRC-ST03), the 5-FU component of ECF is substituted by capecitabine (ECX). The perioperative ECX is to be compared with ECX plus bevacizumab in a phase 3 setting [28•,29].

Adjuvant chemoradiation is also being tested in Europe. In the Dutch CRITICS trial, patients with resectable gastric cancer receive neoadjuvant ECC and surgery, and then either adjuvant ECC or adjuvant 45-Gy radiation with cisplatin and capecitabine [30].

Studies in East Asia

In Korea, where D2 gastrectomy is routinely performed as in Japan, an adjuvant randomized controlled trial is currently evaluating capecitabine/oxaliplatin after curative surgery for stage II and III gastric cancer (CLASSIC trial) [31]. This is an international study involving institutions in China and Taiwan, and would be the last large-scale randomized controlled trial with a control arm of surgery alone (as further discussed in the Future Perspectives section). Adjuvant chemoradiotherapy is being evaluated in the Samsung Medical Center (Seoul, South Korea) a mega-volume center for gastric cancer surgery (1000 gastrectomies/year). The center published a nonrandomized study using the same regimen as the INT 0116 trial, and results suggested the survival benefit of this regimen even after D2 gastrectomy [32•]. Currently, a randomized controlled trial in a single-institutional setting is under way at the Samsung Medical Center to compare D2 gastrectomy plus adjuvant capecitabine/cisplatin with D2 plus chemoradiation [33].

Following the ACTS-GC trial, adjuvant S-1 has become a standard treatment in Japan, and various trials are active or being planned with S-1 as the reference arm. An adjuvant study (SAMIT) is evaluating the sequential use of paclitaxel and S-1 or oral UFT (tegafur–uracil) for T3/T4 gastric cancer in a 2 × 2 factorial design, expecting that adding paclitaxel to a fluoropyrimidine may reduce peritoneal recurrence [34•]. Following the SPIRITS trial, in which the superiority of S-1/cisplatin to S-1 alone was proven for advanced gastric cancer [35], a phase 2 trial is under way to confirm the feasibility of adjuvant S-1/cisplatin after D2 curative gastrectomy for stage III gastric cancer.

Neoadjuvant chemotherapy has also been evaluated in phase 2 settings. The Japan Clinical Oncology Group (JCOG) completed four trials recruiting high-risk gastric cancer patients (ie, linitis plastica, large diffuse ulcerative tumors, or tumors with bulky nodal metastasis). Three regimens were used: S-1 alone, cisplatin/irinotecan, and S-1/cisplatin. A high pathological response rate with low toxicity was observed with S-1/cisplatin, and a phase 3

trial (JCOG 0501) has started to compare immediate D2 gastrectomy plus adjuvant S-1 with neoadjuvant S-1/cisplatin followed by D2 gastrectomy plus adjuvant S-1 [36].

Future Perspectives

Although the treatment modalities and populations studied were all different, the three trials clearly showed a survival benefit of adjuvant or perioperative therapy for gastric cancer. With the exception of the Korean CLASSIC trial, a control arm of surgery alone has already disappeared in recently launched randomized controlled trials [31]. Large-scale trials will be conducted to compare various combinations of chemotherapy and radiotherapy before and/or after surgery, possibly including new molecular targeting agents.

In the West, the American principle of adjuvant chemoradiation and European principle of perioperative chemotherapy will certainly merge in the near future through cooperative randomized controlled trials. The Dutch CRITICS trial is such an example [30]. International cooperation may become mandatory in the West because of the relatively low incidence of gastric cancers, especially those that are localized.

The increasing trend of esophageal adenocarcinoma and esophagogastric junction tumors in the West are also expected to change the target population. In the middle of the trial, MAGIC extended its inclusion criteria to include esophageal cancer. Currently, there are several phase 2 studies that recruit patients with only esophageal and junctional adenocarcinomas. Application of the results of these trials to stomach cancer merits attention.

In Eastern Asia, the evolution of adjuvant therapy is also awaited, but from a different standpoint. In the INT 0116 and MAGIC trials, the 5-year overall survival rates of the surgery groups are less than 30%, even after curative resection. For a population with such a poor prognosis, toxic combination therapy is warranted even despite the possibility of treatment-related death. However, for a population in which a majority survives by surgery alone, physicians may hesitate about the blind use of highly toxic therapy for all patients, especially before surgery. These physicians would likely prefer primary D2 gastrectomy, careful pathological staging, and selection of high-risk tumors for adjuvant therapy. Simple regimens with high compliance and low toxicity are desirable, and in this regard, oral S-1 monotherapy is acceptable.

According to the Japanese Gastric Cancer Association's nationwide registry of gastric cancer, the 5-year overall survival rate of resected stage IIIb and IV tumors (International Union Against Cancer's TNM [tumor, node, metastasis] staging) was 30.5% and 9.9%, respectively; for resected linitis plastica tumors, it was 16.2% [37•]. Together, these populations would have a comparable prognosis to those of the INT 0116/MAGIC trials, and will likely become a target of toxic combination therapy before and/or after surgery. The JCOG 0501 is such an example [36]. Thus, (neo)adjuvant regimens in Japan and Korea will probably evolve depending on tumor stages, based on the premise that D2 gastrectomy provides sufficient local tumor control and accurate staging.

Conclusions

As a result of three pivotal trials, adjuvant and neoadjuvant therapies for gastric cancer have entered a new era. Large-scale, randomized controlled trials should further produce evidence of benefits from various combination regimens. The East and the West have different patient populations and surgical approaches with different baseline survival rates; therefore, despite some cross-over, their studies are likely to move forward in separate directions. Research on molecular prognostic/predictive markers may be helpful in bridging the gap.

Clinical Trials Acronyms

ACTS-GC—Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; CALGB—Cancer and Leukemia Group B; CLASSIC—Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; CRITICS—Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach; INT—Intergroup; JCOG—Japanese Clinical Oncology Group; MAGIC—Medical Research Council Adjuvant Gastric Infusional Chemotherapy; MRC-ST—Medical Research Council Study; REAL—Revised European American Lymphoma Classification; RTOG—Radiation Therapy Oncology Group; SAMIT—Stomach Cancer Adjuvant Multi-institutional Trial; SMC IRB—Samsung Medical Center Institutional Review Board; SPIRITS—S-1 Plus Cisplatin vs S-1 in RCT in the Treatment of Stomach Cancer; SWOG—Southwest Oncology Group.

Disclosure

No potential conflict of interest relevant to this article was reported.

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D2 Lymphadenectomy Alone or with Para-aortic Nodal Dissection for Gastric Cancer

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ABSTRACT

BACKGROUND

Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. Whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival is controversial. We conducted a randomized, controlled trial at 24 hospitals in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer.

METHODS

Between July 1995 and April 2001, 523 patients with curable stage T2b, T3, or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (263 patients) or to D2 lymphadenectomy plus PAND (260 patients). We did not permit any adjuvant therapy before the recurrence of cancer. The primary end point was overall survival.

RESULTS

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (P=0.07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the rate of death was 0.8% in each group). The median operation time was 63 minutes longer and the median blood loss was 230 ml greater in the group assigned to D2 lymphadenectomy plus PAND. The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03 (95% confidence interval [CI], 0.77 to 1.37; P=0.85). There were no significant differences in recurrence-free survival between the two groups; the hazard ratio for recurrence was 1.08 (95% CI, 0.83 to 1.42; P=0.56).

CONCLUSIONS

As compared with D2 lymphadenectomy alone, treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer. (ClinicalTrials.gov number, NCT00149279.)

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GASTRIC CANCER IS THE SECOND LEADING cause of cancer death worldwide, although its incidence is decreasing.[1] About 60% of new cases of gastric cancer occur in eastern Asia; the incidence of new cases in Japan is 100,000 per year. Chemotherapy helps to prolong survival in cases of advanced disease, but surgical resection is the most effective treatment for curable gastric cancer. Reports from the Gastric Cancer Registry and other retrospective studies[2-4] have made radical gastrectomy with extended (D2) removal of regional lymph nodes the standard for the treatment of curable gastric cancer in Japan. Two randomized, controlled European trials that compared the less extended D1 dissection with the D2 procedure failed to show a survival benefit for D2 dissection,[5,6] but lack of experience with the surgical procedure and with postoperative care were thought to account for the poor outcome of patients who underwent D2 lymphadenectomy.[7-9] In 2001, the American Intergroup 0116 study showed that chemoradiotherapy after limited lymphadenectomy (D0 or D1) decreased the local recurrence rate and increased long-term survival,[10] a result suggesting that chemoradiotherapy eliminates the residual lymph-node metastases that could be removed by D2 lymphadenectomy. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure as compared with D1 dissection, with no increase in operative mortality.[11] These trials indicate that adequate local control is essential for the treatment of gastric cancer. Hence, the standard of care for curable gastric cancer in eastern Asia and the United States is either gastrectomy with D2 lymphadenectomy and without postoperative chemoradiation or D0 or D1 gastrectomy with postoperative chemoradiation.[12-14]

Once the gastric tumor invades the subserosa (stage T2b), the serosa (stage T3), or the adjacent structures (stage T4), metastases can spread to the para-aortic lymph nodes, which are termed N3 nodes according to the *Japanese Classification of Gastric Carcinoma*, second English edition,[15] and M1 nodes according to the International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification.[16] In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic region is 10 to 30%.[17-19] Because the 5-year overall survival rate of patients with para-aortic nodal metastases can be as high as 20% after systematic dissection,[20] extensive surgery has been performed in Japan since the 1980s for stage T2b, T3, and T4 gastric cancers. However, to our knowledge there has never been a large prospective study to investigate whether para-aortic nodal dissection (PAND) for gastric cancer has a survival benefit. Here we report the final results of a multi-institutional, randomized, controlled trial by the Japan Clinical Oncology Group (JCOG9501) that was conducted to determine whether the addition of systematic PAND to standard gastrectomy with D2 lymphadenectomy improves survival rates among patients with curable gastric cancer. An interim analysis found no differences between the two procedures in the rates of short-term major complications or in-hospital death.[21]

METHODS

ELIGIBILITY

In this trial, we enrolled patients who were younger than 75 years of age and who had histologically proven gastric adenocarcinoma that was considered potentially curable. Additional eligibility criteria, as determined from intraoperative findings, were the presence of a stage T2b, T3, or T4 tumor, the absence of gross metastases to the para-aortic nodes, and negative cytologic findings in peritoneal-lavage fluid. Diagnosis of metastases by examination of frozen sections of para-aortic nodes was not allowed, because sampling of the nodes would involve dissection. The study protocol was approved by the JCOG protocol review committee and the institutional review boards of each of the 24 participating hospitals. In accordance with JCOG policy in 1995 (the year in which enrollment began), all patients gave written informed consent before undergoing randomization.

RANDOMIZATION AND DATA MANAGEMENT

After confirming the eligibility of the patient during surgery, the surgeon contacted the JCOG Data Center by telephone to receive a randomly generated assignment of the patient to standard D2 lymphadenectomy alone or D2 lymphadenectomy plus PAND. Assignments were made by the minimization method according to clinical T stage (T2b vs. T3 or T4), Borrmann macroscopic type (type 0, 1, or 2 vs. type 3 or 5), and institution (patients with Borrmann type 4 tumors were excluded because there was no chance of cure for such patients if they had para-aortic nodal metastases). The surgeon then performed the assigned operation according to the methods described in the protocol.