系連合学会学術集会、福岡、2012.6.
(350) 八幡和憲、長田真二、山田敦子、加藤順子、棚橋利行、高橋孝夫、山口和也、二村学、吉田和弘：胃癌細胞株に対するVandetanibと5-FUの相乗効果のメカニズム. 第21回日本癌病態治療研究会、群馬、2012.7.
(351) 斎藤史朗、徳丸剛久、大和田昌宏、田中善宏、奥村直樹、野中健一、高橋孝夫、山口和也、長田真二、吉田和弘：pT2 以深胃癌に対する腹腔鏡下胃切除術の成績. 第67回日本消化器外科学会総会、富山、2012.7.
(352) 山口和也、浅井竜一、徳丸剛久、櫻谷卓司、大和田昌宏、斎藤史朗、田中善宏、高橋孝夫、長田真二、吉田和弘：Stage IV 胃癌に対する外科的切除の効果予測. 第67回日本消化器外科学会総会、富山、2012.7.
(353) 奥村直樹、大和田昌宏、斎藤史朗、田中善宏、高橋孝夫、山口和也、長田真二、吉田和弘：鏡視下噴門側胃切除術におけるリンパ節郭清の工夫. 第67回日本消化器外科学会総会、富山、2012.7.
(354) 八幡和憲、長田真二、今井寿、佐々木義之、田中善宏、野中健一、高橋孝夫、山口和也、二村学、吉田和弘：胃癌細胞株に対するVandetanibと5-FU併用による抗腫瘍効果のメカニズム. 第67回日本消化器外科学会総会、富山、2012.7.
(355) 八幡和憲、長田真二、兼松昌子、福田賢也、山田敦子、加藤順子、奥村直樹、松橋延壽、野中健一、高橋孝夫、山口和也、二村学、吉田和弘：胃癌細胞に対するVandetanibと5-FUの相乗効果による新規治療戦略. 第71回日本癌学会学術総会、札幌、2012.9.20
(356) 奥村直樹、山口和也、野中健一、高橋孝夫、長田真二、吉田和弘：当科におけるP0CY1胃癌の検討. (JDDW) 第10回日本消化器外科学会大会、神戸、2012.10.
(357) 松橋延壽、斉藤史郎、田中善宏、奥村直樹、野中健一、高橋孝夫、山口和也、長田真二、吉田和弘：当科における腹腔鏡下胃切除における長期予後についての検討. (JDDW)第10回日本消化器外科学会大会、神戸、2012.10.
(358) 八幡和憲、長田真二、山田敦子、加藤順子、棚橋利行、高橋孝夫、山口和也、二村学、吉田和弘：胃癌細胞株い対するVandetanibと5-FUの相乗効果とそのメカニズム. (JDDW)第10回日本消化器外科学会大会、神戸、2012.10.
(359) 吉田和弘：胃がん. 第50回日本癌治療学会学術集会、 2012.10.25、横浜.
(360) 山口和也、加納寛悠、館正仁、櫻谷卓司、棚橋利行、今井寿、斉藤史郎、佐々木義之、松橋延壽、奥村直樹、長瀬通隆、野中健一、高橋孝夫、長田真二、吉田和弘：StageIV 胃癌に対する手術症例の検討. 第50回日本癌治療学会学術集会、横浜、2012.10.
(361) 松橋延壽、斉藤史郎、奥村直樹、高橋孝夫、山口和也、長田真二、吉田和弘：当科における腹腔鏡下胃切除術における長期予後の検討. 第50回日本癌治療学会学術集会、横浜、2012.10.
(362) 八幡和憲、長田真二、兼松昌子、福田賢也、山田敦子、加藤順子、棚橋利行、田中善宏、奥村直明、松橋延壽、野中健一、高橋孝夫、山口和也、二村学、吉田和弘：胃癌細胞に対するVandetanibと5-FUの相乗効果による新規治療戦略. 第50回日本癌治療学会学術集会、横浜、2012.10.

(363) K. Yoshida, K. Yamaguchi, N. Okumura, T. Takahashi, Y. Tanaka, S. Osada: Surgical treatment of gastric cancer in Japan. 第 50 回日本癌治療学会学術集会、 2012.10.26、横浜.
(364) 吉田和弘、山口和也、奥村直樹、高橋孝夫、田中善宏、長田真二、長瀬通隆：進行・再発胃癌における HER2 検査の実態. 第 50 回日本癌治療学会学術集会、 2012.10.26、横浜.
(365) 奥村直樹、山口和也、斉藤史郎、今井寿、佐々木義之、田中善宏、松橋延壽、野中健一、高橋孝夫、長田真二、吉田和弘：当科における肝転移を伴う StageIV 胃癌に対する治療成績. 第 50 回日本癌治療学会学術集会、横浜、2012.10.
(366) 八幡和憲、長田真二、兼松昌子、福田賢也、山田敦子、加藤順子、棚橋利行、田中善宏、奥村直樹、松橋延壽、野中健一、高橋孝夫、山口和也、二村学、吉田和弘：消化器がんに対する Vandetanib と 5-FU の相乗効果とメカニズム解析. 第 23 回日本消化器癌発生学会総会、徳島、2012.11.
(367) 松橋延壽、加納寛悠、館正仁、櫻谷卓司、棚橋利行、今井寿、佐々木義之、斉藤史郎、田中善宏、奥村直樹、野中健一、高橋孝夫、山口和也、長田真二、吉田和弘：当科における胃 GIST に対して腹腔鏡手術症例の検討. 第 74 回日本臨床外科学会総会、東京、2012.12.
(368) 吉田和弘、坂下文夫、山本淳史、尾関豊、山口和也、奥村直樹、竹村博文、北島康夫、山田實紘：Robotic surgery による胃切除導入に際してのこつと pitfall. 第 25 回日本内視鏡外科学会総会、 2012.12.6、横浜
(369) 山口和也、今井寿、佐々木義之、田中善宏、奥村直樹、松橋延壽、野中健一、高橋孝夫、長田真二、吉田和弘：当科における腹腔鏡下胃切除術の手術成績と長期予後. 第 25 回日本内視鏡外科学会総会、横浜、2012.12.
(370) 奥村直樹、山口和也、館正仁、櫻谷卓司、棚橋利行、今井寿、佐々木義之、田中善宏、松橋延壽、野中健一、高橋孝夫、長田真二、吉田和弘：当科における腹腔鏡噴門側胃切除術の検討. 第 25 回日本内視鏡外科学会総会、横浜、2012.12.
(371) 八幡和憲、長田真二、福田賢也、兼松昌子、山田敦子、加藤順子、棚橋利行、田中善宏、奥村直樹、松橋延壽、野中健一、高橋孝夫、山口和也、二村学、吉田和弘：消化器癌に対する Vandetanib と 5-FU の相乗効果. 第 25 回日本バイオセラピィ学会学術集会総会、倉敷、2012.12.
(372) 水口知香、稲田高男、松下尚之：4 型胃癌に対する治療成績の向上に関する検討. 第 85 回日本胃癌学会、2013.2. 大阪
(373) 浅生義人、安藤恭久、西内綾、西野裕人、奥村晋也、藤浩明、錦織達人、加藤滋、門川佳央、近藤正人、待本貴文、古山裕章、吉村玄浩：当院の腹腔鏡補助下胃全摘術の成績について. 第 25 回日本内視鏡外科学会総会、2012.12、横浜.
(374) 近藤正人、安藤恭久、西内綾、西野裕人、奥村晋也、藤浩明、錦織達人、政野裕紀、佐々木勉、待本貴文、浅生義人、山之口賢、古山裕章、吉村玄浩：腹腔鏡補助下幽門側胃切除術での RY 再建. 第 66 回に本消化器外科学会総会、2011.7、名古屋.
(375) 西野裕人、安藤恭久、西内綾、奥村晋也、藤浩明、錦織達人、政野裕紀、

佐々木勉、近藤正人、待本貴文、浅生義人、山之口賢、古山裕章、吉村玄浩：化学療法により門脈腫瘍塞栓が消失し切除しえたAF産生胃癌の1例．第73回日本臨床外科学会総会、2011.11、東京.

(376) 矢田匡、錦織達人、佐々木勉、西野裕人、安藤恭久、西内綾、奥村晋也、藤浩明、政野裕紀、近藤正人、待本貴文、浅生義人、山之口賢、古山裕章、吉村玄浩：TS-1/CDDP療法による術前化学療法で組織学的 CR を得た進行胃癌の一例．第73回日本臨床外科学会総会、2011.11、東京.

(377) 藤浩明、西野裕人、安藤恭久、西内綾、奥村晋也、錦織達人、政野裕紀、佐々木勉、近藤正人、待本貴文、浅生義人、山之口賢、古山裕章、吉村玄浩：幽門側胃切除、BillrothⅡ法再建40年後に輸入脚の穿孔をきたした1例．第73回日本臨床外科学会総会、2011.11、東京.

(378) 浅生義人、安藤恭久、西野裕人、西内綾、奥村晋也、藤浩明、錦織達人、政野裕紀、佐々木勉、近藤正人、待本貴文、山之口賢、古山裕章、吉村玄浩：当院の OrVil を用いた腹腔鏡補助下胃全摘術の再建における工夫．第24回日本内視鏡外科学会総会、2011.12、大阪.

(379) 浅生義人、安藤恭久、西内綾、西野裕人、奥村晋也、藤浩明、錦織達人、政野裕紀、佐々木勉、近藤正人、待本貴文、山之口賢、古山裕章、吉村玄浩：当院の胃癌術前化学療法の現状について．第35回京大関連施設外科研究会、2012.1、京都.

(380) 浅生義人、安藤恭久、西内綾、西野裕人、奥村晋也、藤浩明、錦織達人、政野裕紀、佐々木勉、近藤正人、待本貴文、山之口賢、古山裕章、吉村玄浩：腹腔鏡補助下胃全摘術の安全性についての検討．第84回日本胃癌学会総会、2012.2、大阪.

(381) 近藤正人、安藤恭久、西内綾、西野裕人、奥村晋也、藤浩明、錦織達人、政野裕紀、佐々木勉、待本貴文、浅生義人、山之口賢、古山裕章、吉村玄浩：OrVil を用いた食道先行切離による腹腔鏡補助下胃全摘術の安定した再建．第84回日本胃癌学会総会、2012.2、大阪.

(382) K. Ito, T. Nishigori, Y. Asao, M. Kondo, T. Yoshimura: A case of metachronous colon metastasis from gastric cancer. 第84回日本胃癌学会総会、2012.2、大阪.

(383) 中森幹人，辻俊明，岩橋誠，中村公紀，尾島敏康，飯田武，勝田将裕，松村修一，早田啓治，谷眞至，川井学，瀧藤克也，山上裕機：固形癌の環境破壊機能を有する腫瘍溶解ウイルス製剤の開発．第112回日本外科学会，2012.4，幕張.

(384) 中村公紀，岩橋誠，中森幹人，尾島敏康，勝田将裕，飯田武，辻俊明，早田啓治，松村修一，川井学，谷眞至，瀧藤克也，山上裕機：胃癌に対する脾門リンパ節転移の予測因子と郭清の意義．第112回日本外科学会，2012.4，幕張.

(385) 早田啓治，岩橋誠，尾島敏康，勝田将裕，飯田武，中森幹人，中村公紀，上田健太郎，宮澤基樹，辻俊明，川井学，谷眞至，瀧藤克也，山上裕機：癌微小環境で産生される炎症性サイトカイン IL－17 を標的とした新規腫瘍免疫療法の開発．第112回日本外科学会，2012.4，幕張.

(386) 松村修一，中森幹人，岩橋誠，中村公紀，尾島敏康，飯田武，勝田将裕，

辻　俊明，早田啓治，山上裕機：胃癌における Beclin-1 の発現とオートファジー誘導に関する基礎的・臨床的検討．第 112 回日本外科学会，2012.4，幕張．
(387) 辻俊明，岩橋誠，中森幹人，中村公紀，尾島敏康，勝田将裕，飯田武，早田啓治，松村修一，山口俊介，谷眞至，川井学，瀧藤克也，山上裕機：CY 陽性単独の非治癒切除胃癌症例の臨床病理学的検討．第 112 回日本外科学会，2012.4，幕張．
(388) 早田啓治，岩橋誠，尾島敏康，勝田将裕，飯田武，中森幹人，中村公紀，宮澤基樹，辻俊明，上田健太郎，山上裕機：癌微小環境で産生される炎症性サイトカイン IL－17 の制御は腫瘍浸潤リンパ球の細胞傷害活性を増強する．第 33 回癌免疫外科研究会，2012.5，横浜．
(389) 中森幹人，岩橋誠，辻俊明，松村修一，中村公紀，尾島敏康，飯田武，勝田将裕，早田啓治，山上裕機：消化器癌に対する機能付加型ウイルス製剤の基礎的研究開発．第 67 回日本消化器外科学会，2012.7，富山．
(390) 辻俊明，岩橋誠，中森幹人，中村公紀，尾島敏康，飯田武，勝田将裕，早田啓治，松村修一，山上裕機：審査腹腔鏡による胃癌腹膜播種診断と治療成績．第 67 回日本消化器外科学会，2012.7，富山．
(391) 竹内昭博，中村公紀，飯田武，岩橋誠，中森幹人，尾島敏康，勝田将裕，辻　俊明，松村修一，山上裕機：CDDP 投与を契機に SIADH を発症した進行胃癌の 2 例．第 67 回日本消化器外科学会，2012.7，富山．
(392) 中村公紀，岩橋誠，中森幹人，尾島敏康，勝田将裕，飯田武，辻俊明，松村修一，瀧藤克也，山上裕機：超音波内視鏡は胃癌の術前診断に有用か？—1044 例からの解析—．第 67 回日本消化器外科学会，2012.7，富山．
(393) 尾島敏康，瀧藤克也，中村公紀，岩橋誠，中森幹人，勝田将裕，飯田武，山上裕機：胃 ESD に伴う合併症の解析．第 84 回日本消化器内視鏡学会，2012.10，神戸．
(394) M. Nakamori, M. Iwahashi, T. Tsuji, S. Matsumura, T. Ojima, T. Iida, M. Nakamura, M. Katsuda, K. Hayata, Y. Ino, T. Todo, H. Yamaue: Therapeutic enphancement via an armed oncolytic herpes simplex virus expressing thrombospondin-1 for human gastric cancer. The 71st Annual Meeting of the Japanese Cancer Association, 2012.9, Sapporo.
(395)T. Ojima, M. Iwahashi, M. Nakamori, M. Nakamura, M. Katsuda, T. Iida, K. Hayata, T. Naka, T. Tsuji, S. Matsumura, T. Kato, K. Ueda, H. Yamaue: Association of allogeneic blood transfusions and long-term survival of gastric cancer patients. The 71st Annual Meeting of the Japanese Cancer Association, 2012.9, Sappor.
(396) 岩崎善毅、大橋学、岩永知大、大日向玲紀、高橋慶一、山口達郎、松本寛、中野大輔：高度進行胃癌に対する術前化学療法.第 112 回日本外科学会定期学術集会、千葉、2012 年 4 月．
(397) 岩崎善毅、大橋学、岩永知大:StageⅣ胃癌に対する術前化学療法と手術療法による集学的治療.第 10 回日本消化器外科学会大会、神戸、2012 年 10 月．
(398) 二宮基樹，丁田泰宏，金澤卓，藤原康宏,原野雅生,松川啓義,小島康知,塩

崎滋弘, 大野　聡:癌の局所制御を目指した大動脈周囲リンパ節郭清術（ビデオワークショップ）.　第 84 回日本胃癌学会総会、2012.2、大阪.

(399) 二宮基樹, 丁田泰宏, 金澤卓, 藤原康宏,原野雅生,松川啓義,小島康知,塩崎滋弘, 大野　聡:胃癌手術における再建法と機能評価（ビデオシンポジウム）. 第 112 回日本外科学会定期学術集会、2012.4、千葉.

(400) 二宮基樹, 丁田泰宏, 金澤卓:膜構造と「起点」「受け」「底」を意識した胃癌リンパ節郭清. 第 20 回日本消化器関連学会集会　2012.10、神戸.

(401) 衛藤剛、猪股雅史、白石憲男、北野正剛: Alexa Fluor 488 付加制限増殖型レオウイルスを用いた新しいトレーサーの開発.第 71 回日本がん学会学術総会. 2012.9.19-21 札幌.

(402) 草野徹、上田貴威、當寺ヶ盛学、白下英史、衛藤剛、猪股雅史、野口剛、白石憲男、北野正剛: 膵上縁リンパ節転移を有する進行胃癌の病理学的特徴. 第 10 回日本消化器外科学会. 2012.10.10-13 神戸.

(403) 原田勝久、野口剛、柴田智隆、上田貴威、衛藤剛、猪股雅史、白石憲男、北野正剛: 腹膜播種再発に対してイマチニブが奏効している小腸 GIST の 1 例.　第 50 回日本癌治療学会. 2012.10.25-27 横浜.

(404) 赤木智徳、猪股雅史、衛藤剛、野口剛、白石憲男、北野正剛: 大腸がん患者におけるリンパ節転移および予後不良の指標としての Visinin-like protein-1 (VSNL-1)発現の有用性. 第 23 回日本消化器癌発生学会. 2012.11.15-16 徳島.

(405) 衛藤剛、白石憲男、北野正剛: 腹腔鏡補助下幽門側胃切除術の進行胃癌に対する適応拡大の検証：多施設共同ランダム化第Ⅱ相試験. 第 25 回日本内視鏡外科学会総会. 2012.12.6-8 横浜.

## H. 知的財産権の出願・登録状況
## (予定を含む)

### 1. 特許取得
該当するもの無し

### 2. 実用新案登録
該当するもの無し

### 3. その他
該当するもの無し

研究成果の刊行に関する一覧表

雑誌

| 発表者氏名 | 論文タイトル名 | 発表誌名 | 巻号 | ページ | 出版年 |
|---|---|---|---|---|---|
| The GASTRIC (Global Advanced /Adjuvant Stomach Tumor Research International Collaboration) Group | Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer. | JAMA | 303(17) | 1729-1737 | 2010 |
| Fukagawa T., Katai H., Saka M., Morita S., Sasajima Y., Taniguchi H., Sano T., Sasako M. | Significance of Lavage Cytology in Advanced Gastric Cancer Patients. | World J Surg | 34 | 563-568 | 2010 |
| Yoshikawa T., Omura K., Kobayashi O., Nashimoto A., Takabayashi A., Yamada T., Yamaue H., Fuji M., Yamaguchi T., Nakajima T. | A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). | Eur J Surg Oncol | 36(6) | 546-551 | 2010 |
| Makino T., Fujiwara Y., Takiguchi S., Miyata H., Yamasaki M., Nakajima K., Nishida T., Mori M., Doki Y. | The utility of pre-operative peritoneal lavage examination in serosa-invading gastric cancer patients. | Surgery | 148(1) | 96-102 | 2010 |
| Seiji Ito, Yasuhiro Kodera, Yoshinari Mochizuki, Taiki Kojima, Hayao Nakanishi, Yoshitaka Yamamura | Phase II clinical trial of postoperative S-1 monotherapy for gastric cancer patients with free intraperitoneal cancer cells detected by real-time RT-PCR. | World J Surg | 34 | 2083-2089 | 2010 |

| | | | | | |
|---|---|---|---|---|---|
| Tanizawa Y., Terashima M. | Lymph node dissection in the resection of gastric cancer: review of existing evidence. | Gastric Cancer | 13(3) | 137-148 | 2010 |
| 笹子三津留 | 胃癌成績向上をめざした集学的治療と個別化手術と周術期化学療法をめぐる話題 | 胃がん perspective | 13(2) | 136-139 | 2010 |
| 伊藤誠二 | 胃がんに対する補助化学療法 2)胃がんにおける術前化学療法の臨床試験 | 腫瘍内科 | 5(4) | 374-379 | 2010 |
| 野村栄治、李相雄、徳原孝哉、谷川允彦 | 進行胃癌の治療戦略 | 外科 | 72(7) | 697-702 | 2010 |
| 吉川貴己, 青山徹, 渡辺隆文, 林勉, 尾形高士, 長晴彦, 円谷彰, 小林理 | 微小な腹膜転移(Minimal Peritoneal Metastasis: MPM)を伴うスキルス胃癌の予後からみた外科切除の意義 | 癌と化学療法 | 37(12) | 2264-2266 | 2010 |
| 寺島雅典、徳永正則、谷澤豊、板東悦郎、川村泰一、近藤潤也、三木友一朗、幕内梨恵、山川雄士、杉沢徳彦、瀧雄介、茂木陽子、大島令子、絹笠祐介、金本秀行、上坂克彦 | がん治療のエビデンスと臨床試験　胃癌 | 外科治療 | 103(2) | 115-123 | 2010 |
| 寺島雅典、板東悦郎、徳永正則、谷澤豊、川村泰一、近藤潤也、杉沢徳彦、瀧雄介、大島令子、茂木陽子、三木友一朗、山川雄士、幕内梨恵、絹笠祐介、金本秀行、上坂克彦、安井博史、朴成和 | 腹腔洗浄細胞診陽性例に対する肉眼的治癒切除の意義 | 癌の臨床 | 56(4) | 291-295 | 2010 |

| | | | | | |
|---|---|---|---|---|---|
| D. Takahari, T. Hamaguchi, K. Yoshimura, H. Katai, S. Ito, N. Fuse, T. Kinoshita, H. Yasui, M. Terashima, M. Goto, N. Tanigawa, K. Shirao, T. Sano, M. Sasako | Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. | Cancer Chemother Pharmacol | 67(6) | 1423- 1428 | 2011 |
| I. Miyashiro, H. Furukawa, M. Sasako, S. Yamamoto, A. Nashimoto, T. Nakajima, T. Kinoshita, O. Kobayashi, K. Arai, the Gastric Cancer Surgical Study Group in the Japan Clinical Oncology Group | Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa- positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2. | Gastric Cancer | 14(3) | 212-218 | 2011 |
| M. Sasako, S. Sakuramoto, H. Katai, T. Kinoshita, H. Furukawa, T. Yamaguchi, A. Nashimoto, M. Fujii, T. Nakajima and Y. Ohashi | Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer. | Journal of Clinical Onocology | 29(33) | 4387-4393 | 2011 |
| Moon JH, Fujiwara Y, Nakamura Y, Okada K, Hanada H, Sakakura C, Takiguchi S,Nakajima K, Miyata H, Yamasaki M, Kurokawa Y, Mori M, Doki Y | REGIV as a potential biomarker for peritoneal dissemination in gastric adenocarcinoma. | J Surg Oncol | 105 | 189-194 | 2011 |
| K. Inoue, Y. Nakane, M. Kogire, K. Fujitani, Y. Kimura, H. Imamura, S. Tamura, S. Okano, A.H. Kwon, Y. Kurokawa, T. Shimokawa, H. Takiuchi, T. Tsujinaka, H. Furukawa | Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer. | Eur J Surg Oncol | 38 | 143-149 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Aoyama, T, Yoshikawa T, Watanabe T, Hayashi T, Ogata T, Cho H, Tsuburaya A | Macroscopic tumor size as an independent prognostic factor for stage II/III gastric cancer patients who underwent D2 gastrectomy followed by adjuvant chemotherapy with S-1. | Gastric Cancer | 14(3) | 274-8 | 2011 |
| Aoyama T, Yoshikawa T, Watanabe T, Hayashi T, Ogata T, Cho H, Tsuburaya A | Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1. | Gastric cancer | 14(2) | 150-4 | 2011 |
| 黒川幸典、土岐祐一郎、笹子三津留 | 胃癌の外科治療に関する臨床試験 | 臨床外科 | 66(5) | 582-586 | 2011 |
| 堀高明、小澤りえ、花山寛之、山下英孝、海辺展明、大嶋勉、竹村雅至、菊池正二郎、笹子三津留 | 胃癌における術後補助化学療法の現状と今後の展望 | 癌と化学療法 | 38(9) | 1390-1395 | 2011 |
| 藪崎裕、梨本篤 | 脾温存胃全摘術におけるリンパ節郭清手技－当院における工夫－ | 外科治療 | 105(6) | 572-579 | 2011 |
| 吉田和弘, 山口和也, 高橋孝夫 | 消化管がんの術前・術後補助化学療法の新展開 | 日本医師会雑誌 | 140(8) | 1691-1695 | 2011 |
| 寺島雅典、坂東悦郎、永正則、谷澤豊、川村泰一、近藤潤也、杉沢徳彦、瀧雄介、大島令子、茂木陽子、三木祐一朗、山川雄士、幕内梨恵、絹笠祐輔、金本秀行、上坂克彦、安井博史、朴成和 | Stage IV胃癌における外科治療の有用性　腹腔洗浄細胞診陽性例に対する肉眼的治癒切除の意義 | 癌の臨床 | 56(4) | 291-295 | 2011 |

| | | | | | |
|---|---|---|---|---|---|
| 小寺泰弘, 藤原道隆, 伊藤誠二, 大橋紀文, 中尾昭公 | Stage IV胃癌における胃切除後の化学療法「昔ながらの戦略」の実力は? | 癌の臨床 | 56(4) | 283-289 | 2011 |
| M. Sasako | Gastric Cancer Eastern Experience. | Surg Oncol Clin N Am | 21(1) | 71-7 | 2012 |
| T. Yoshikawa, M. Sasako | Gastrointestinal Cancer: Adjuvant chemotherapy after D2 gastrectomy for gastric cancer. | Nature Reviews Clinical Oncology l | 9 | 192-4 | 2012 |
| Ishida K, Nishizuka S , Chiba T , Ikeda M , Kume K , Endo F , Katagiri H , Matsuo T , Noda H , Iwaya T , Yamada N , Fujiwara H , Takahashi M , Itabashi T , Uesugi N , Maesawa C , Tamura G , Sugai T , Otsuka K , Koeda K , Wakabayashi G | Molecular Marker Identification for Relapse Prediction in 5-FU-Based Adjuvant Chemotherapy in Gastric and Colorectal Cancers. | PloS ONE | 7(8) | e43236 | 2012 |
| Hirao M, Tsujinaka T, Imamura H, Kurokawa Y, Inoue K, Kimura Y, Shimokawa T, Furukawa H | Overweight is a risk factor for surgical site infection following distal gastrectomy for gastric cancer. Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG). | Gastric Cancer | in press | | 2012 |
| Hayashi T, Yoshikawa T, Aoyama T, Ogata T, Cho H, Tsuburaya A | Severity of complications after gastrectomy in elderly patients with gastric cancer. | World journal of surgery | 36(9) | 2139-45 | 2012 |

| | | | | | |
|---|---|---|---|---|---|
| Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M | Poor Survival Rate in Patients with Postoperative Intra-Abdominal Infectious Complications Following Curative Gastrectomy for Gastric Cancer. | Annals of Surgical Oncology | in press | | 2012 |
| Sugisawa N, Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M | Intra-abdominal infectious complications following gastrectomy in patients with excessive visceral fat. | Gastric Cancer | 15(2) | 206-212 | 2012 |
| 石山泰寛，稲木紀幸，野 宏成，松永 正，北村祥貴、山本道宏，小竹優範、黒川勝、伴登宏行，山田哲司 | S-1+CDDPによる進行胃癌に対する術前化学療法の検討. | 癌と化学療法 | 39(13) | 2517-2519 | 2012 |
| 岩崎善毅、大橋学、岩永知大、大日向玲紀、高橋慶一、山口達郎、松本寛、中野大輔 | 高度進行胃がんに対する化学療法後の局所療法としての大動脈周囲リンパ節郭清の意義. | 癌と化学療法 | 39(12) | 2319-2320 | 2012 |

# Ⅲ. 研究成果の刊行物・別刷

「がん臨床研究事業」

研究代表者　笹子　三津留

# Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer: A Meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group

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http://jama.ama-assn.org/cgi/content/full/303/17/1729

REVIEW

# Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

## A Meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group*

**Context** Despite potentially curative resection of stomach cancer, 50% to 90% of patients die of disease relapse. Numerous randomized clinical trials (RCTs) have compared surgery alone with adjuvant chemotherapy, but definitive evidence is lacking.

**Objectives** To perform an individual patient-level meta-analysis of all RCTs to quantify the potential benefit of chemotherapy after complete resection over surgery alone in terms of overall survival and disease-free survival, and to further study the role of regimens, including monochemotherapy; combined chemotherapy with fluorouracil derivatives, mitomycin C, and other therapies but no anthracyclines; combined chemotherapy with fluorouracil derivatives, mitomycin C, and anthracyclines; and other treatments.

**Data Sources** Data from all RCTs comparing adjuvant chemotherapy with surgery alone in patients with resectable gastric cancer. We searched MEDLINE (up to 2009), the Cochrane Central Register of Controlled Trials, the National Institutes of Health trial registry, and published proceedings from major oncologic and gastrointestinal cancer meetings.

**Study Selection** All RCTs closed to patient recruitment before 2004 were eligible. Trials testing radiotherapy; neoadjuvant, perioperative, or intraperitoneal chemotherapy; or immunotherapy were excluded. Thirty-one eligible trials (6390 patients) were identified.

**Data Extraction** As of 2010, individual patient data were available from 17 trials (3838 patients representing 60% of the targeted data) with a median follow-up exceeding 7 years.

**Results** There were 1000 deaths among 1924 patients assigned to chemotherapy groups and 1067 deaths among 1857 patients assigned to surgery-only groups. Adjuvant chemotherapy was associated with a statistically significant benefit in terms of overall survival (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.76-0.90; $P<.001$) and disease-free survival (HR, 0.82; 95% CI, 0.75-0.90; $P<.001$). There was no significant heterogeneity for overall survival across RCTs ($P=.52$) or the 4 regimen groups ($P=.13$). Five-year overall survival increased from 49.6% to 55.3% with chemotherapy.

**Conclusion** Among the RCTs included, postoperative adjuvant chemotherapy based on fluorouracil regimens was associated with reduced risk of death in gastric cancer compared with surgery alone.

*JAMA. 2010;303(17):1729-1737* www.jama.com

ALTHOUGH EPIDEMIOLOGICAL studies describe a reduction in recent years in gastric cancer incidence, gastric cancer is a common and highly fatal disease, with current 5-year survival rates less than 20%.[1] Surgery for disease at an early stage can usually be performed with curative intent, but the 5-year survival rate is disappointing.[2,3] Over the last 3 decades, numerous phase 3 studies including a surgery-only group have been reported, but definitive evidence of the efficacy of adjuvant chemotherapy is lacking. Recently, the large-scale Japanese phase 3 trial by the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) group[4] reported the superiority of S-1 as an adjuvant chemotherapy over surgery alone after D2 lymph node dissection. Its applicability outside of East Asia is uncertain, and the First-Line Advanced Gastric Cancer Study (FLAGS) in advanced disease[5] that compared cisplatin and S-1 vs cisplatin and fluoropyridines in non-Asian countries was negative. Therefore, standard management following curative surgery is heterogeneous throughout the world.

**See also pp 1723, 1753 and Patient Page.**

No patient-level meta-analyses have been carried out to date. Based on published results, recent meta-analyses[6-10] indicated that adjuvant chemotherapy produces a small survival benefit, if any, in patients with resected gastric carcinoma (eTable 1, available at http://www.jama.com) but did not recommend adjuvant chemotherapy as routine therapy. Since then, several additional trials have been conducted in this setting. Overall,

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the results of some of these trials were promising but inconsistent when all trials were considered. Therefore, it was deemed important to assess the benefit of adjuvant chemotherapy quantitatively through an exhaustive meta-analysis based on individual patient data from all relevant trials.

## METHODS

Data from all published randomized trials comparing adjuvant chemotherapy with surgery alone for resectable gastric cancers were sought electronically. The strategy filter for computerized bibliographic searches of MEDLINE (1970 to 2009) is described in the eMethods (available at http://www.jama.com). No restriction on language of publication was considered. The Cochrane Central Register of Controlled Trials, the National Institutes of Health trial registry (ClinicalTrials.gov), and proceedings books from major oncologic and gastrointestinal cancer meetings were also examined for published results. To ensure that all relevant trials were included, researchers with expertise in the area were queried for the existence of unpublished trials. Four groups of regimens were specified in the protocol: trials investigating (1) monochemotherapy agents; (2) fluorouracil, mitomycin C, and other therapies without anthracyclines; (3) fluorouracil, mitomycin C, and anthracyclines; and (4) other polychemotherapy regimens.

### Study Selection and Data Extraction

Trials were eligible if they were randomized, they ended patient recruitment before 2004, and they compared any adjuvant therapy after curative resection vs surgery alone. Trials investigating immunotherapy or neoadjuvant or perioperative chemotherapy were excluded. Likewise, trials with radiotherapy or intraperitoneal chemotherapy were not in the scope of our research.

The following data were requested for all individual patients: center, randomization date, date of last follow-up (or date of death), survival status, cause of death, relapse status, type and date of relapse if any, TNM stage, overall stage grouping system, performance status (World Health Organization or Karnofsky index), and age at entry. Because the International Union Against Cancer modified the staging system in 1997, stages measured with the old system were expressed according to the new classification. Updated survival status and date of last follow-up were requested from the trialists. Data for patients excluded from the analysis after randomization were obtained whenever possible.

Overall survival (OS) was defined as the time from randomization to death from any cause or to the last follow-up that was used as a date of censoring. Disease-free survival (DFS) was the time to relapse, second cancer, or death from any cause, whichever came first. Detailed information on the type of relapse was not always available. All data were centrally reanalyzed and checked for inconsistencies. In particular, diagnostic tools for randomization quality were systematically applied.[11]

### Statistical Methods

Time-related end points (OS and DFS) were analyzed through log-rank tests, with trial as stratification factor. We used a fixed-effects model and the inverse variance method where the weight of each trial was proportional to the variance of the observed minus expected number of events.[12] Heterogeneity between trials and groups of trials (eg, defined by different chemotherapy regimens) was tested using $\chi^2$ statistics[13] and measured with the $I^2$ statistic.[14] Forest plots were used to display hazard ratios (HRs) within individual trials and overall. Within each trial, HRs were estimated without adjusting for any covariates. When a statistically significant effect was detected, the increase in survival probabilities or absolute benefit at 5 or 10 years after randomization was computed based on the estimates of the survival curves. Estimates of the survival curves used the actuarial approach adjusted for trial proposed by the Early Breast Cancer Trialists' Collaborative Group,[15] yielding a representation consistent with the main log-rank analyses stratified by trial. Their interpretations are similar to the Kaplan-Meier curves.

The hypothesis of proportional hazards was explored graphically and tested by using the Grambsch and Therneau test[16] with linear residual relation and by including a time-dependent covariate in a stratified Cox model. We further investigated the hazard functions through time in each group under study. Median follow-up was estimated using the reversed Kaplan-Meier function.[17] All patients were included in the analyses as randomly assigned based on an intention-to-treat principle, whether or not they were analyzed in the trial publication. In cases where survival data were missing, those patients were excluded from the analysis.

As a sensitivity analysis we investigated the overall treatment effect in all the identified trials, pooling individual patient data with summary statistics extracted from the publication.[18] We also analyzed these summary statistics separately. In addition, we investigated heterogeneity among the regions where the trials were conducted (Europe, Asia, and the United States). All $P$ values were 2-sided at the 5% level, and confidence intervals (CIs) had 2-sided probability coverage of 95%. SAS version 9.1 (SAS Institute, Cary, North Carolina) was used with macros developed at the European Organization for Research and Treatment of Cancer Data Center (Brussels, Belgium) for meta-analysis and at Institut Gustave-Roussy (Villejuif, France) for survival curves. Hazard functions were plotted with Stata version 9.2 (StataCorp, College Station, Texas). All the results were discussed during 4 large international investigators' meetings organized in different countries.

## RESULTS

Thirty-one trials that had randomized 6390 patients were identified (FIGURE 1). We obtained individual data for 3838 patients included in 17 trials (TABLE). This represents 60% of the targeted

data. Corresponding authors of the eligible trials were contacted at least 5 times each between January 2007 and February 2010. Data were not obtained for 2552 patients in 14 trials because of no reply or a refusal to share data from the principal investigator[35-39] or because data were lost or inaccessible.[40-48] One trial[21] compared surgery alone against 2 investigational groups with fluorouracil or ftorafur. Both groups were pooled. Central randomization was reported in 14 trials (with block stratification for 8 and minimization for 6). All trials were open without blinding procedures. No trials were found to have major inconsistencies in the randomization procedure, and no difference in follow-up could be detected between the 2 groups.

### Patient Characteristics

The characteristics of the 3838 randomly assigned patients are listed by group (eTable 2) and chemotherapy regimen (eTable 3). There were no major differences in patient characteristics between treatment groups. The eTables also show summary statistics on the clinical outcomes of interest: median OS and median DFS. Fifty-seven patients (1.5%) with missing survival data were excluded from analyses (date of randomization, last status, and last date were missing for 25, 8, and 49 patients, respectively). They were balanced between the 2 groups (28 patients with chemotherapy vs 29 patients with surgery only). We identified 361 patients and 103 deaths with a last date after the publication date of the related trial.

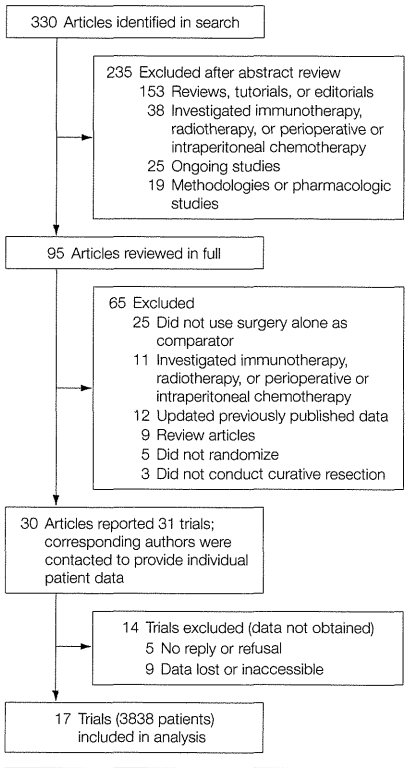
### Any Adjuvant Chemotherapy vs Surgery Alone

Median follow-up for OS was slightly different between the 2 groups (7 years; range, 0.1-28.2 years in the surgery-only group vs 7.2 years; range, 0.1-30.3 years; $P<.001$), during which 1067 patients in the surgery-only group and 1000 patients in the chemotherapy group died. FIGURE 2 shows the HRs for OS in the individual trials and overall. There was a significant benefit from any chemotherapy compared with surgery alone, with an overall HR of death equal to 0.82 (95% CI, 0.76-0.90; $P<.001$), corresponding to an overall 18% reduction of the hazard with chemotherapy. The estimated median OS was 4.9 years (95% CI, 4.4-5.5) in the surgery-only group vs 7.8 years (95% CI, 6.5-8.7) in the group receiving adjuvant chemotherapy. Absolute benefits were 5.8% at 5 years (from 49.6% to 55.3%) and 7.4% at 10 years (from 37.5% to 44.9%) (FIGURE 3). No significant heterogeneity (variability of trial-specific HRs) was apparent across the set of trials ($P=.52$). Globally, there were no time trends in the treatment effect according to the year of last inclusion ($P=.82$). Similarly, no significant heterogeneity was detected across the 3 continents ($P=.27$) (eFigure 1, available at http://www.jama.com).

As a sensitivity analysis, we combined summary statistics extracted from unavailable trials with the collected individual patient data for a total of 5866 patients and 28 trials. For 3 trials,[43,44,47] no summary statistics could be extracted from the report. Neither the general conclusions nor the magnitude of the observed treatment effect (HR, 0.82; 95% CI, 0.77-0.88; $P<.001$) were modified (eFigure 2). Analysis of the 11 trials with available summary resulted in an HR of 0.81 (95% CI, 0.73-0.91; $P<.001$). No significant heterogeneity was detected ($P=.11$).

Disease-free survival was available on a subset of 14 trials with a total number of 3297 patients from the 21 trials that collected this information, representing 78% of the targeted number of patients. On this subpopulation, we observed an HR of death of 0.85 (95% CI, 0.77-0.93), consistent with the estimate on the full database. Hazard ratios for DFS in individual trials and overall are shown in FIGURE 4. Adjuvant chemotherapy improved DFS compared with surgery alone with an overall HR of 0.82 (95% CI, 0.75-0.90; $P<.001$). The absolute benefit at 5 years was 5.3%, from 48.7% to 54.0% (eFigure 3). There was no indication of heterogeneity between trials in treatment effect ($P=.57$).

**Figure 1.** Study Flowchart




### Analysis of Groups of Regimens

An interaction test between the type of regimen (monochemotherapy; fluorouracil and mitomycin C with anthracyclines; fluorouracil, mitomycin C, and others without anthracyclines; other polychemotherapy) and the treatment effect on OS and on DFS were not significant ($P=.13$ for both). In the sensitivity analysis, interaction was of borderline significance for OS ($P=.05$). We further explored these 4 groups. Survival curves are provided as supplementary material (eFigures 4 through 7).

**Monochemotherapies.** The 2 medium-sized trials[19,20] (1 European, 1 Japanese) included a total of 324 patients of whom 317 patients were eligible for the meta-analysis with OS data. They showed a statistically significant benefit of adjuvant monochemotherapy over surgery alone (HR, 0.60; 95% CI, 0.42-0.84; $P=.03$), with 5-year survival rates of

**Table.** List of the Included Randomized Trials

| Source | Adjuvant Chemotherapy | Dosage | Schedule | Patients, No. CT (n = 1953) | Patients, No. S (n = 1885) | Recruitment Period | UICC Stage, % | Follow-up, Median (Range), y |
|---|---|---|---|---|---|---|---|---|
| Monochemotherapy | | | | (n = 163) | (n = 161) | | | |
| Grau et al,[19] 1993 | Mitomycin C | 20 mg/m$^2$ IV (day 1) | Every 6 wk (4 cycles) | 68 | 66 | 1977-1983 | I, 14; II, 32; III, 54 | 11.2 (0.8-20.1) |
| Nakajima et al,[20] 2007 | Uracil plus tegafur | 360 mg/m$^2$/d orally | Every wk (16 mo) | 95 | 95 | 1987-2001 | II, 75; III, 25 | 6.0 (1.2-8.4) |
| Polychemotherapies: fluorouracil + mitomycin C + others without anthracyclines | | | | (n = 572) | (n = 481) | | | |
| Nakajima et al,[21] 1984[a] | Mitomycin C<br>Fluorouracil or ftorafur<br>Cytosine arabinoside<br>Fluorouracil or ftorafur | 1.3 mg/m$^2$ IV<br>167 mg/m$^2$ or 267 mg/m$^2$ IV<br>13 mg/m$^2$ IV, then orally<br>133 mg/m$^2$ or 670 mg/m$^2$ | Twice a week for 5 wk<br>Twice a week for 5 wk<br>Twice a week for 5 wk<br>For 2 y | 156 | 72 | 1974-1977 | I, 46; II, 29; III, 21; X, 4 | 24.2 (11.4-30.3) |
| Nakajima et al,[22] 1999 | Mitomycin C<br>Fluorouracil<br>Uracil plus tegafur | 1.4 mg/m$^2$ IV<br>166.7 mg/m$^2$ IV<br>300 mg/m$^2$/d orally | Mitomycin C and fluorouracil: for the first 3 wk<br>Oral uracil plus tegafur: for the next 18 mo | 288 | 285 | 1988-1992 | I, 90; II, 9; III, 1 | 6.7 (2.9-8.6) |
| Nashimoto et al,[23] 2003 | Mitomycin C<br>Fluorouracil<br>Cytosine arabinoside<br>Fluorouracil | 1.3 mg/m$^2$ IV<br>167 mg/m$^2$ IV<br>13 mg/m$^2$ IV<br>134 mg/m$^2$ orally | Fluorouracil IV: for the first 3 wk<br>Fluorouracil orally: for the next 18 mo | 128 | 124 | 1993-1994 | I, 94; II, 6 | 5.9 (2.7-8.2) |
| Polychemotherapies: fluorouracil + mitomycin C + anthracyclines | | | | (n = 497) | (n = 516) | | | |
| Coombes et al,[24] 1990 | Fluorouracil<br>Doxorubicin<br>Mitomycin C | 600 mg/m$^2$ IV<br>30 mg/m$^2$ IV<br>10 mg/m$^2$ IV | 8-wk cycle (6 cycles) | 133 | 148 | 1981-1984 | I, 20; II, 24; III, 40; IV: 16 | 13.0 (0.1-21.6) |
| Lise et al,[25] 1995 | Fluorouracil<br>Doxorubicin<br>Mitomycin C | 400 mg/m$^2$ IV<br>40 mg/m$^2$ IV<br>10 mg/m$^2$ IV | Every 6 wk (7 cycles) | 155 | 159 | 1979-1989 | I, 17; II, 25; III, 40; IV, 18 | 6.5 (0.9-12.3) |
| Macdonald et al,[26] 1995 | Fluorouracil<br>Doxorubicin<br>Mitomycin C | 600 mg/m$^2$ IV<br>30 mg/m$^2$ IV<br>10 mg/m$^2$ IV | 8-wk cycle (6 cycles) | 109 | 112 | 1978-1991 | I, 19; II, 41; III, 40 | 16.6 (2.9-23.9) |
| Tsavaris et al,[27] 1996 | Fluorouracil<br>Epirubicin<br>Mitomycin C | 600 mg/m$^2$ IV<br>30 mg/m$^2$ IV<br>10 mg/m$^2$ IV | 8-wk cycle (3 cycles) | 47 | 45 | 1988-1994 | I, 16; II, 39; III, 45 | 4.9 (0.6-6.2) |
| Popiela et al,[28] 2004[b] | Fluorouracil<br>Doxorubicin<br>Mitomycin C | 600 mg/m$^2$ IV<br>30 mg/m$^2$ IV<br>10 mg/m$^2$ IV | 8-wk cycle (6 cycles) | 53 | 52 | 1988-1992 | III, 76; IV, 24 | 13.0 (2.5-15.5) |
| Other polychemotherapies | | | | (n = 721) | (n = 727) | | | |
| Douglass and Stablein,[29] 1982 | Semustine<br>Fluorouracil | 150 mg/m$^2$ orally<br>325 mg/m$^2$ IV<br>325 mg/m$^2$ IV | Every 10 wk (for 2 y) | 91 | 88 | 1975-1980 | NA | 12.1 (2.2-13.9) |
| Engstrom et al,[30] 1985 | Semustine<br>Fluorouracil<br>Fluorouracil | 150 mg/m$^2$ orally<br>350 mg/m$^2$ IV<br>375 mg/m$^2$ IV | Day 1<br>Every 10 wk (for 2 y) | 100 | 96 | 1975-1980 | NA | 16.5 (0.4-24.9) |
| Krook et al,[31] 1991 | Fluorouracil<br>Doxorubicin | 350 mg/m$^2$ IV<br>40 mg/m$^2$ IV | 5 d every mo (3 cycles) | 63 | 64 | 1979-1989 | NA | 15.6 (5.7-19.8) |
| Bajetta et al,[32] 2002 | Etoposide<br>Doxorubicin<br>Cisplatin<br>Leucovorin<br>Fluorouracil | 120 mg/m$^2$ IV<br>20 mg/m$^2$ IV<br>40 mg/m$^2$ IV<br>100 mg/m$^2$ IV<br>375 mg/m$^2$ IV | For 2 cycles | 135 | 136 | 1994-1997 | I, 8; II, 31; III, 51; IV, 10 | 6.2 (0.1-9.5) |
| Bouché et al,[33] 2005 | Fluorouracil<br>Cisplatin | 800 mg/m$^2$ IV then 1 g/m$^2$<br>100 mg/m$^2$ IV | 5 d<br>Every 4 wk (4 cycles) | 138 | 140 | 1989-1997 | I, 34; II, 29; III, 25; IV, 12 | 8.1 (0.4-12.7) |
| Nitti et al,[34] 2006[c] | Fluorouracil<br>Doxorubicin<br>Methotrexate with leucovorin | 1.5 g/m$^2$ IV<br>30 mg/m$^2$ IV<br>1.5 g/m$^2$ IV with 15 mg/m$^2$ (oral or IV) | For 6 cycles | 103 | 103 | 1991-1998 | I, 13; II, 25; III, 61; IV, 1 | 7.0 (2.6-11.3) |
| Nitti et al,[34] 2006[c] | Fluorouracil<br>Epirubicin<br>Methotrexate with leucovorin | 1.5 g/m$^2$ IV<br>70 mg/m$^2$ IV<br>1.5 g/m$^2$ IV with 30 mg/m$^2$ (oral or IV) | For 6 cycles | 91 | 100 | 1990-1998 | I, 9; II, 87; IV, 4 | 6.9 (0.5-11.1) |

Abbreviations: CT, chemotherapy; IV, intravenous; NA, not available; S, surgery alone; UICC, International Union Against Cancer.
[a] Investigated 2 regimens; in the second one, ftorafur replaced fluorouracil. The data are pooled.
[b] Investigated chemotherapy + bacille Calmette-Guerin in a third group that was not included.
[c] Relied on a combined analysis of 2 databases that are analyzed separately.

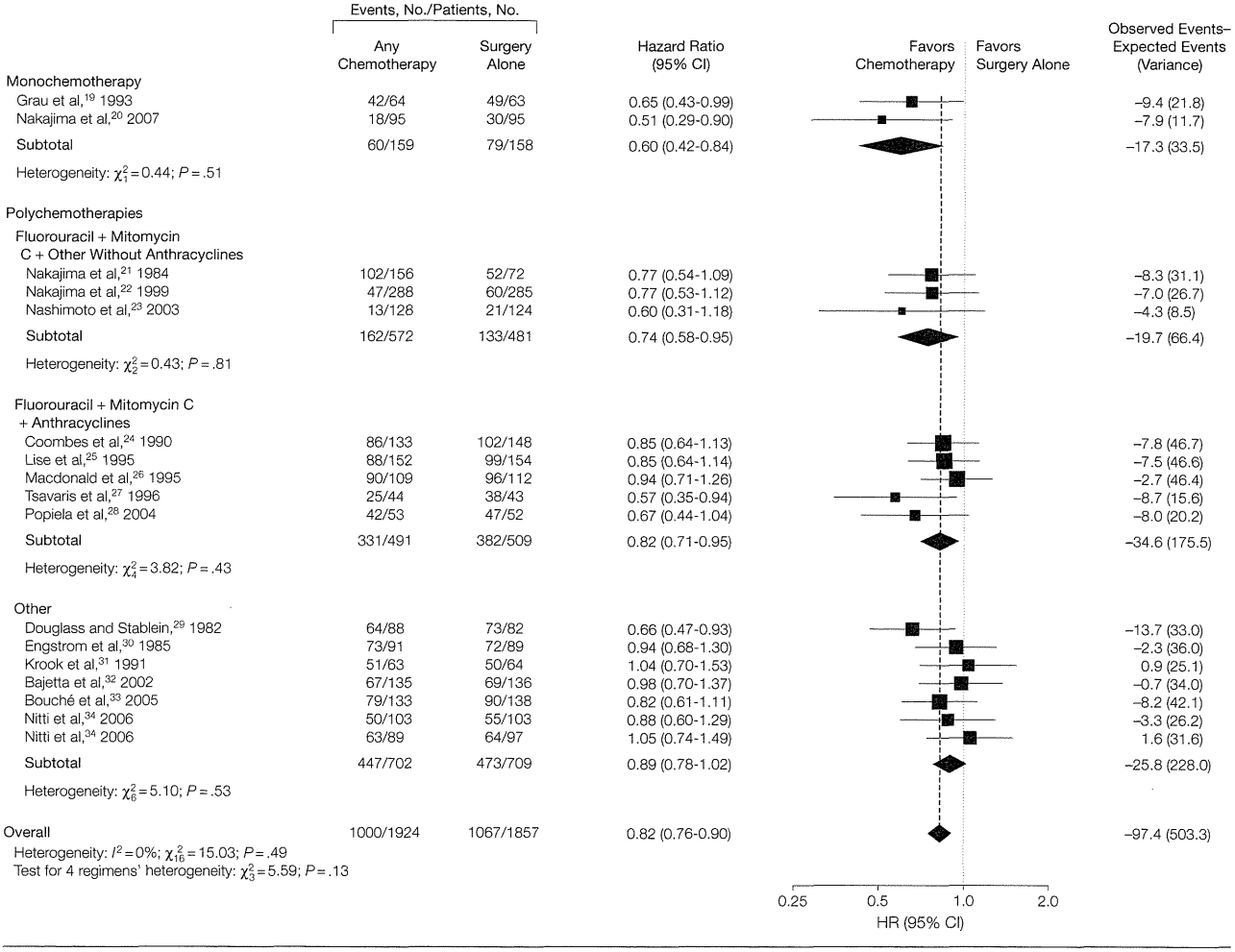
53.9% for the surgery-only group vs 71.4% for the chemotherapy group. This rate was much higher than in the whole meta-analysis, suggesting that these patients had a good baseline prognosis. Disease-free survival was not collected in 1 of the 2 trials and hence not analyzed.

**Polychemotherapies: Fluorouracil + Mitomycin C + Others Without Anthracyclines.** Three Japanese trials with 1053 patients total used combined chemotherapy including fluorouracil derivatives, mitomycin C, and others without anthracyclines.[21-23] Overall, a statistically significant benefit for OS was observed (HR, 0.74; 95% CI, 0.58-0.95; $P=.03$), with 5-year survival rates of 76.6% for the surgery-only group vs 82.8% for the chemotherapy group. A similar effect on DFS was observed in the 2 more recent studies (HR, 0.69; 95% CI, 0.48-0.98) with 5-year DFS rates of 84.2% for the surgery-only group vs 88.2% for the chemotherapy group.

**Polychemotherapies: Fluorouracil + Mitomycin C + Anthracyclines.** Five trials (4 European, 1 US) using combined chemotherapy including anthracyclines had 1013 patients total and 1000 patients with OS data.[24-28] Overall, a statistically significant hazard reduction was observed for OS (HR, 0.82; 95% CI, 0.71-0.96; $P=.01$). The 5-year survival rate increased from 31.9% to 39.3%, and heterogeneity was not detected ($P=.52$). The HR for DFS was estimated from 4 trials. The risk of relapse or second primary cancer or death was also statistically significantly reduced (HR, 0.80; 95% CI, 0.69-0.94; $P=.006$) with 5-year DFS rates of 31.9% for the surgery-only group vs 39% for the chemotherapy group.

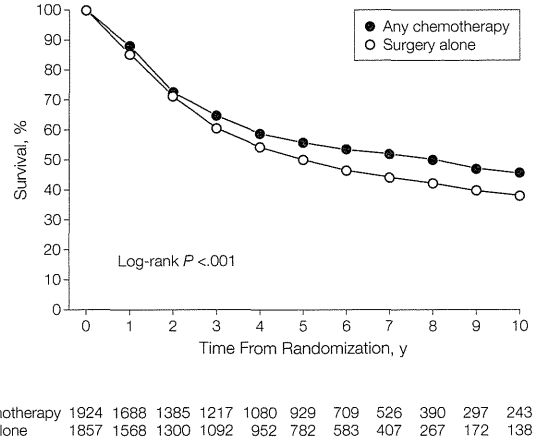
**Polychemotherapies: Group "Other" vs Surgery Alone.** For 1411 of 1448 patients in 7 trials for whom survival data were available,[29-34] we did not detect a

**Figure 2.** Individual Trial and Overall Hazard Ratio for Overall Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone




The inverse of the variance of observed events minus expected events measures the weight of each trial in the analysis. *P* values are from *P*-for-effect modification testing for heterogeneity within or across the groups of regimens. The sizes of data markers are proportional to the number of deaths in the trials. CI indicates confidence interval; HR, hazard ratio.

**Figure 3.** Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years




The estimates of the survival curves use an actuarial approach as described in the Methods.

significant effect of adjuvant regimens vs surgery alone (HR, 0.89; 95% CI, 0.78-1.02; $P=.09$). The 5-year survival rate was 41.5%. Heterogeneity was not detected ($P=.51$) even though 1 trial[29] that used fluorouracil and semustine showed a significant treatment effect. Five-year DFS was 41.9% for the surgery-only group vs 44.5% for the chemotherapy group, and a marginally significant effect of treatment on DFS was observed (HR, 0.88; 95% CI, 0.78-1.0; $P=.05$), which was mainly driven by the positive study[29]; in a sensitivity analysis excluding this trial, the DFS effect was not significant (HR, 0.91; 95% CI, 0.79-1.04; $P=.18$).

### Proportionality of the Hazard Functions

Plots of survival curves for all chemotherapy regimens combined or in each regimen group suggested nonproportional hazard functions, as illustrated by late separation of the survival function estimates. Nonproportional hazards were not detected using the Grambsch and Therneau test ($P=.35$). When a time-dependent model was fitted on the full data set with a cut-point at 2 years, treatment effect before and after 2 years was significantly different ($P<.001$). Point estimates of the HR by 2-year intervals showed a regular decrease from 0.91 in the first 2 years from randomization to 0.75 between 2 and 4 years and 0.62 beyond 4 years. After 8 years, the number of events became too small to provide meaningful estimates. Because these cut-points were derived from the data, they should be considered with caution. Hazard functions showed that the rate of death reached a peak at 18 months and steadily decreased thereafter to reach a plateau at about 5 years (eFigure 8).

## COMMENT

Adjuvant chemotherapy without radiation for gastric cancer has recently become the standard of care in Japan after the publication of the results of the ACTS-GS trial reporting on S-1[4] but not in Europe or the United States. Numerous randomized phase 2 and phase 3 trials have produced conflicting results. However, many of these trials had limited sample sizes, making it difficult to draw definitive conclusions. Based on the individual data of 3838 patients from 17 different trials with a median follow-up longer than 7 years, the largest patient-level meta-analysis performed so far, we showed a modest but statistically significant benefit associated with adjuvant chemotherapy after curative resection of gastric cancers. The mortality hazard was reduced by about 18% and an absolute improvement of about 6% in OS was observed after 5 years. This improvement was maintained at 10 years. An 18% reduction in the risk of relapse, second primary, or death was also observed. This treatment benefit was maintained in 3 of the 4 investigated groups of fluorouracil-based regimens, with reductions in the risk of death ranging from 20% to 40% (nonstatistically significant heterogeneity). Only 1 trial[19] that enrolled 134 patients investigated a non–fluoropyrimidines-based regimen. Sensitivity analysis excluding this trial led to the same results. The absence of interaction with the class of regimen and with the region as well as the long follow-up is reassuring. Patient-level meta-analyses are the most reliable means to provide an exhaustive and unbiased summary of the available evidence on a clinical question of interest and complete large well-conducted trials (such as those that are currently done).

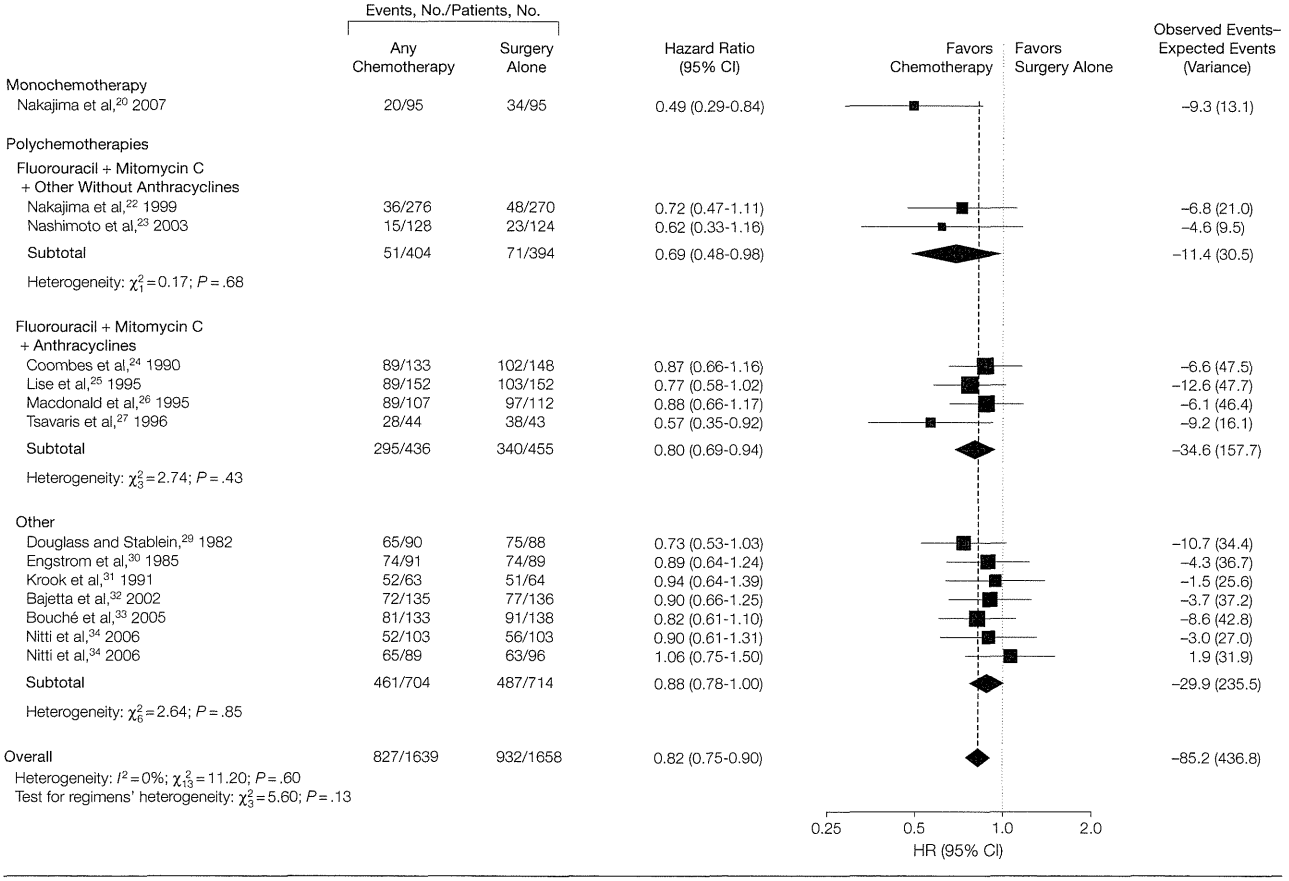
Postoperative chemotherapy is not the only adjuvant treatment for gastric cancer. In 2001, results of a trial that randomized between surgery and surgery with chemoradiotherapy showed an absolute increase in median survival of 9 months.[49] Thereafter, chemoradiation therapy has gained popularity and has been increasingly used as a standard of care, especially in the United States, even though the optimal chemotherapy regimen has not been identified yet. Several trials are currently being conducted to explore this issue, but their results will not be available until 2011. Similarly, neoadjuvant trials have shown the benefit of starting the chemotherapy treatment as early as possible.[50-52] Although the short-term results of delayed surgery are being debated,[53] neoadjuvant treatment, which can be administered to more patients than postoperative chemotherapy, has gained acceptance in western countries.

We could only collect about two-thirds of all data available from randomized trials in early gastric cancer, which is disappointing in view of the intensive efforts made at repeatedly contacting the principal investigators of the trials. However, for all but 3 trials with unavailable individual patient data, we could extract summary statistics from the published articles. Our results remained unchanged when these summary statistics were included in the calculations. Combining unverified published summary statistics with carefully checked individual patient data is not a satisfactory way of estimating an unbiased overall treatment effect, but it provides a way of assessing the robustness of a meta-analysis with respect to unavailable trials.

The optimal design of future adjuvant gastric cancer clinical trials, particularly the choice of an adequate control group, is a delicate issue. It is beyond the scope of our meta-analysis to identify the optimal regimen; however, based on our data, chemotherapy seems justified as a control group. Fluoropyrimidines-based regimens, in particular the oral forms (uracil plus tegafur and recently S-1 monotherapy) that have been shown to be better tolerated,[8] seem reasonable treatment options, although their applicability outside East Asian countries remains uncertain. This raises the question of why fluoropyrimidines (intravenous fluorouracil or oral tegafur) appear to have activity in the adjuvant setting for gastric cancer as well as in colon cancer even though their efficacy is disappointing for the treatment of advanced disease.

In conclusion, this patient-level meta-analysis shows that adjuvant fluorouracil-based chemotherapy, even in monotherapy, is associated with improvement in overall survival (HR, 0.82) and is recommended for patients who have not received perioperative treatments after complete resection of their gastric cancer. Future reports based on data being collected will explore prognostic factors and the surrogacy of disease-free survival for overall survival in this population.

**Figure 4.** Individual Trial and Overall Hazard Ratio for Disease-Free Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone




The inverse of variance of observed events minus expected events measures the weight of each trial in the analysis. *P* values are from *P*-for-effect modification testing for heterogeneity within or across the groups of regimens. The sizes of the data markers are proportional to the number of events. CI indicates confidence interval; HR, hazard ratio.