The Role of Radiation Therapy in Upper Gastrointestinal Cancers

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Abstract: Upper gastrointestinal cancers are common and account for a high proportion of cases of cancer-related morbidity and mortality. Combined-modality therapy with surgery, chemotherapy, and radiation therapy is standard treatment for esophageal and gastroesophageal junction cancers. For gastric cancer, the need to include radiation therapy appears to depend on the quality of the surgery performed. Radiation therapy plays an uncertain role in the surgical management of pancreatic cancer, and the results of ongoing clinical trials are awaited. Retrospective studies support the inclusion of radiotherapy in the surgical management of biliary tract cancers. The development of more effective systemic therapy for upper gastrointestinal cancers may ultimately lead to a greater survival benefit due to the potential for improved local tumor control achieved with radiotherapy.

Introduction

Cancers of the upper gastrointestinal (UGI) tract are common globally and account for a disproportionately high incidence of cancer-related mortality. Nearly 150,000 cases of UGI cancer were diagnosed in the United States in 2016, and UGI cancers accounted for 8.7% of all cancer diagnoses and 16.6% of all cancer-related deaths.[1] The nearly 100,000 deaths per year from UGI cancers translates into a fatality rate of 67%, with the highest mortality rates seen in esophageal (93%) and pancreatic cancers (79%).

Modest progress has been made in the treatment of UGI cancers. The addition of adjuvant chemotherapy to surgery has improved survival in esophagogastric and pancreatic cancers, with a less certain benefit for systemic therapy in biliary and gallbladder cancers. The role of radiation combined with the surgical management of UGI cancers is the subject of this review.

Is Radiation Therapy Needed as Part of Surgical Management?

Surgical management of UGI cancers seeks to achieve a negative-margin resection of the primary tumor and the clearance of regional lymph nodes. Systemic therapy is added to reduce metastatic disease recurrence rates and may have a lesser effect on local recurrence rates. For cancers in which systemic therapy is less effective

in metastatic disease, adjuvant chemotherapy may have a lesser effect in reducing systemic disease recurrence. Radiation therapy is given to reduce local disease recurrence, and radiation may be more strongly considered in cancers with a high risk for local recurrence. Patients who have cancers with a relatively low rate of local recurrence after surgery may not benefit from postoperative radiation. When surgery is performed by less experienced surgeons, the rates of negative surgical margins may be lower and the rates of lymph node retrieval inadequate, leading to higher rates of local tumor recurrence. On the other hand, for cancers in which metastatic disease tends to develop, the incremental improvements in local tumor control achieved with radiation after surgery may not translate into a survival benefit.

Because patients may not be able to tolerate therapy after surgery for UGI cancers, and given that upfront surgery to clear the primary tumor may fail, radiation as preoperative rather than postoperative therapy has been extensively studied. Advantages of a preoperative approach include better patient tolerance of therapy, downstaging of the primary tumor, enhancement of surgical resection rates, and assessment of the response to treatment in the resected tumor specimen. Also, patients whose cancer may disseminate early in the course of preoperative treatment may be spared the rigors of surgical resection, particularly those with cancers in which metastatic disease tends to develop early. Disadvantages of preoperative therapy include the risk for disease progression during ineffective treatment, a delay in local tumor control that can compromise the patient's nutritional status, and the potential for the overtreatment of patients with earlier-stage disease that is overstaged during clinical pretherapy staging. Nonetheless, an increasing shift to the preoperative use of chemotherapy and radiation therapy in UGI cancers has been taking place.

Esophageal and Gastroesophageal Junction Cancers

Cancers of the esophagus and gastroesophageal junction (GEJ) are uncommon in the West, where the predominant histology is adenocarcinoma. Squamous cancer remains the most common histology worldwide, with the highest incidence in East Asia. Esophageal cancer is the world's sixth leading cause of cancer-related death.[2] The complex anatomy of the mediastinum and GEJ increases the risk for inadequate surgical resection and potentially the risk for local tumor recurrence, factors that account for increases in surgical morbidity and mortality. Long-term survival rates reported in surgical series from the 1970s were as low as 5%[3]; 5-year survival approaches 20% in US studies conducted in the 2000s.[4] High recurrence rates for both local and systemic disease have led to relatively poor outcomes with surgical management alone.

Practice varies globally in the management of esophageal squamous cell carcinoma and adenocarcinoma. Results from controlled trials evaluating the use of preoperative chemotherapy, primary chemoradiotherapy without surgery, and preoperative chemoradiotherapy in esophageal cancer are outlined in Table 1. For squamous cancer treated in East Asia, preoperative chemotherapy followed by surgery remains the therapy standard at many centers.[5] However, perioperative chemotherapy for both esophageal squamous cancer and adenocarcinoma failed to improve any outcome compared with surgery alone in USA Intergroup 113 (Radiation Therapy Oncology Group trial 8911).[6] USA Intergroup 113 treated 443 patients with 3 preoperative and 2 postoperative cycles of a continuous infusion of fluorouracil (5-FU) combined with cisplatin (CF). The trial reported poor rates of R0 resection with (63%) and without chemotherapy (59%), high rates of local tumor recurrence (27% and 29%) after curative surgery, and a poor 5-year survival rate of 20% with or without chemotherapy.

Other trials have also indicated poor results for preoperative chemotherapy in esophageal cancer, including the 802-patient OEO2 trial in esophageal cancer from the United Kingdom Medical Research Council.[7,8] Although touted as a positive trial for preoperative CF, poor rates of R0 resection were seen with (60%) and without chemotherapy (54%), and high rates of local recurrence after curative surgery were also reported (31% vs 32%). In long-term follow-up, a marginal improvement in 5-year overall survival of 6% was achieved with preoperative chemotherapy (17% and 23%),[8] with no effect of chemotherapy on rates of distant recurrence. The 6% improvement in the rate of R0 resection was attributed to a benefit of preoperative chemotherapy. The FNCLCC/FFCD (Fédération Nationale des Centres de Lutte Contre le Cancer/Fédération Francophone de Cancérologie Digestive) trial from France treated 224 patients with adenocarcinoma of the lower esophagus, GEJ, or stomach with preoperative and postoperative CF.[9] This trial, the outlier in these series treating primarily esophageal cancer, found improvements in R0 resection (13%) and survival (13%) with preoperative chemotherapy in esophageal and GEJ adenocarcinoma. However, even this trial reported high rates of local tumor recurrence after surgery (29% and 36%).

Concern about the adequacy of preoperative chemotherapy alone in patients with esophageal cancer has been underscored by reports of persistently poor rates of R0 resection for esophageal and GEJ cancers. These have occurred even in contemporary trials, and despite careful preoperative staging with endoscopic ultrasound, positron emission tomography (PET), and laparoscopy.

Table 1. Selected Results of Phase 3 Trials of Preoperative or Perioperative Chemotherapy and Chemoradiotherapy in Esophageal and Gastroesophageal Junction Cancer

Trial	Treatment	Histology	N	R0 Resection Rate	Pathologic CR Rate	Survival		Local Failure Rate
						Median	Overall	
INT-0113[6]	Periop 5-FU/Cis + Surgery	Adeno + SCC	213	62%	2.5%	14.9 mo	3-y, 23%	32%
	Surgery	227	59%	N/A	16.1 mo	3-y, 26%	31%	
OEO2[7,8]	Preop 5-FU/Cis + Surgery	Adeno + SCC	400	60%	NS	16.8 mo	5-y, 23%	19%
	Surgery		402	54%	N/A	13.3 mo	5-y, 17%	17%
FNCLCC/ FFCD[9]	Periop 5-FU/Cis + Surgery	Adeno	109	87%	NS	NS	5-y, 38%	24%
	Surgery		110	74%	N/A	NS	5-y, 24%	26%
RTOG 8501[12,13]	5-FU/Cis + RT	SCC + Adeno	61	—	—	12.5 mo	5-y, 26%	56%
	RT		63	—	—	8.9 mo	5-y, 0%	68%
CROSS[17,18]	Preop Carbo/Pac + RT + Surgery	SCC + Adeno	178	92%	29%	49.4 mo	5-y, 47%	22%
	Surgery		188	69%	N/A	24.0 mo	5-y, 33%	37%

Adeno, adenocarcinoma; Carbo, carboplatin; Cis, cisplatin; CR, complete response; 5-FU, 5-fluorouracil; mo, months; N, number of patients; N/A, not applicable; NS, not stated; Pac, paclitaxel; Periop, perioperative; Preop, preoperative; RT, radiotherapy; SCC, squamous cell carcinoma; y, year.

In 2 trials from the United Kingdom, which were recently reported in abstract form, 1900 patients received preoperative chemotherapy, including 1600 patients with esophageal and GEJ adenocarcinoma.[10,11] Patients were treated with preoperative CF or ECF (epirubicin/CF). Despite contemporary staging, these trials reported persistently dismal rates of R0 resection (57% and 67%) with preoperative chemotherapy. The alarming results have led to questions about the adequacy of preoperative chemotherapy without radiation therapy, and they underscore the potential need to include preoperative radiation therapy to ensure at least a curative resection in patients with tumors involving the esophagus and GEJ.

The landscape for esophageal cancer treatment changed in 1992 with publication of the Radiation Therapy Oncology Group (RTOG) 8501 trial. This landmark trial indicated that combining 2 cycles of CF chemotherapy with 50 Gy of concurrent radiation therapy and then administering 2 cycles of chemotherapy after radiation therapy, without surgery, achieved a curative outcome in patients with esophageal squamous cancer.[12] The importance of concurrent chemotherapy and radiotherapy was clear; no patients treated with radiation therapy alone survived beyond 3 years. At long-term follow-up, 26% of the patients treated with combined chemoradiotherapy had achieved 5-year survival. This largely occurred in patients with squamous cancer, but a measurable long-term survival was also achieved in the patients with adenocarcinoma.[13] There were high rates of both local persistence and recurrence of disease after chemoradiotherapy (52%), supporting the need for surgery after chemoradiotherapy.

Randomized trials of chemoradiotherapy alone or followed by surgery, largely in squamous cancer, have found that an improvement in local tumor control with surgery after chemoradiotherapy does not always translate into an improvement in survival compared with primary chemoradiotherapy alone.[14,15] These trials support a more selective application of surgery after chemoradiotherapy, perhaps limited to patients with biopsy-positive locally persistent disease. Treatment guidelines indicate that primary chemoradiotherapy without surgery is an acceptable therapy alternative if a clinical complete response to chemoradiotherapy is achieved.[16] High rates of distant recurrence of disease, with or without surgery, should also temper the universal application of surgery to all patients with squamous cell cancer.

The role of surgery for adenocarcinomas of the esophagus and GEJ is less controversial. The combination of chemotherapy and radiotherapy followed by surgery for esophageal and GEJ adenocarcinomas has emerged as an international standard of care since results were reported from the contemporary CROSS trial (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study).[17,18] CROSS compared preoperative weekly carboplatin, paclitaxel, and 41.4 Gy of radiotherapy followed by surgery with surgery alone in esophageal

and GEJ adenocarcinoma and squamous cell carcinoma. In addition to increasing the 5-year survival from 33% to 47%, preoperative therapy led to higher rates of R0 resection (92% vs 69%) and relatively low rates of local recurrence (14% vs 34%). Many feel that this trial established the benchmark treatment for esophageal and GEJ adenocarcinoma. The high rates of pathologic complete response (23% for adenocarcinoma, 49% for squamous cancer) have indicated that this regimen, especially in squamous cancer, also can be used as definitive, nonoperative chemoradiotherapy. Because of the particularly high survival benefit seen in squamous cancers, this trial has revisited the argument for a greater use of surgery after chemoradiotherapy in esophageal squamous cancer.

Additional chemotherapy cycles beyond 2 cycles of CF,[10] the addition of epirubicin to 5-fluorouracil/cisplatin,[10] and the addition of induction chemotherapy cycles before chemoradiotherapy[19] all have failed to improve survival. The benefit of preoperative chemotherapy may be achieved with relatively brief exposure. The recent addition of novel targeted agents to chemoradiotherapy also has failed to improve outcomes. Two trials adding the epithelial growth factor receptor (EGFR)–targeted agent cetuximab (Erbitux, Lilly) to chemoradiotherapy[20,21] failed to improve any outcomes. A pilot trial combining the VEGF-targeted agent bevacizumab (Avastin, Genentech) with chemoradiotherapy,[22] and a randomized trial adding bevacizumab to preoperative chemotherapy,[11] also failed to improve outcome. The RTOG 1010 (Radiation Therapy, Paclitaxel, and Carboplatin With or Without Trastuzumab in Treating Patients With Esophageal Cancer; NCT01196390) trial recently evaluated the addition of trastuzumab (Herceptin, Genentech) to preoperative carboplatin, paclitaxel, and radiation therapy in human epidermal growth factor receptor 2 (HER2)–positive esophageal and GEJ cancers, and results are expected within the next 1 to 2 years.

An ongoing trial of GEJ and gastric cancer, TOPGEAR (Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma; NCT01924819), is evaluating the use of perioperative ECF chemotherapy with or without preoperative radiotherapy. Other trials evaluating preoperative chemotherapy with or without radiotherapy in esophageal and GEJ cancers include a German trial comparing preoperative 5-FU, oxaliplatin, and docetaxel with the CROSS approach (NCT02509286) and an Irish study comparing preoperative ECF chemotherapy with the CROSS approach (NCT01726452). In the United States, a trial using response on PET scan to guide the selection of chemotherapy during preoperative chemoradiotherapy was recently completely. Results should be reported in 2017 (NCT01333033).

Gastric Cancer

Gastric cancer is the third leading cause of cancer-related mortality globally, with a high incidence in East Asia, eastern Europe, and South America.[23] There is consensus that surgical management should combine subtotal or total gastrectomy with D2 lymph node resection, which encompasses nodes of the greater and lesser curvature, taken in a D1 resection, in addition to gastrohepatic, celiac, and splenic nodes.[24] The adequacy of the surgical resection in gastric cancer may explain the relative contribution of adjuvant chemotherapy and radiotherapy to surgical resection.

Perioperative or postoperative chemotherapy is now a global standard of care. Adjuvant therapy trials involving chemotherapy and radiation therapy are outlined in Table 2. The seminal MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial of perioperative chemotherapy in gastric cancer, conducted by Cunningham and colleagues in the United Kingdom, was first reported in 2006.[25] Patients with adenocarcinoma of the lower third of the esophagus, GEJ, or stomach were eligible; most of the 503 patients treated (74%) had gastric primary tumors. Patients were treated either with upfront surgery or with 3 cycles of ECF chemotherapy followed by surgery and then 3 additional cycles of ECF after surgery. Comparable rates of R0 resection were reported in the preoperative therapy arm (69%) and surgery-alone arm (66%), with esophagogastrectomy or D1 resection performed in 43% to 44% of patients and D2 resection in 40% to 42% of patients. Overall survival was superior for the chemotherapy arm (36% vs 23% at 5 years). Based on this trial, preoperative and postoperative chemotherapy for gastric cancer is a care standard in western Europe and the United States.

Contemporary randomized trials from Japan and Korea in which D2 resection was mandatory before trial entry also have found a survival benefit for adjuvant postoperative chemotherapy. The ACTGS (Adjuvant Chemotherapy for Gastric Cancer With S-1) trial from Japan[26] treated more than 1000 patients either with surgery or with surgery followed by 1 year of S-1 (tegafur, gimeracil, and oteracil) chemotherapy. The 5-year survival improved from 61% to 72% with adjuvant therapy. Supportive evidence for a benefit of adjuvant chemotherapy after D2 gastrectomy also comes from the CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Gastric Cancer) trial from Korea.[27] After D2 gastrectomy, more than 1000 patients received either observation alone or treatment with eight 3-week cycles of oxaliplatin combined with capecitabine. The 5-year overall survival was increased from 69% to 78% with adjuvant chemotherapy. Western treatment guidelines now acknowledge postoperative

Table 2. Trials of Adjuvant Chemotherapy With or Without Radiation Therapy in Gastric Cancer

Trial	N	Treatment	PFS or DFS Rate	5-y OS Rate
MAGIC[25]	250	ECF → Surgery → ECF	PFS HR, 0.66	36.3%
	253	Surgery	—	23.0%
ACTGS[26]	515	Surgery → S-1	65%	72%
	519	Surgery	53%	61%
CLASSIC[27]	520	Surgery → Cape/Oxali	68%	78%
	515	Surgery	53%	69%
INT-0116[29,30]	281	Surgery → 5-FU/FA + RT	3-y DFS, 48%	3-y OS, 50%
	275	Surgery	3-y DFS, 31%	3-y OS, 41%
ARTIST[31,32]	230	Cape/Cis + RT	DFS HR, 0.740	75%
	228	Cape/Cis	—	73%
CRITICS[33]	332	ECC → Surgery → Cape/Cis + RT	5-y DFS, 39.5%	40.9%
	316	ECC → Surgery → ECC	5-y DFS, 38.5%	40.8%

Cape, capecitabine; Cis, cisplatin; DFS, disease-free survival; ECC, epirubicin, cisplatin, capecitabine; ECF, epirubicin, cisplatin, 5-fluoruoracil; FA, folinic acid; HR, hazard ratio; N, number of patients; Oxali, oxaliplatin; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; S-1, tegafur, gimeracil, oteracil; →, followed by.

adjuvant chemotherapy as an acceptable therapy option after D2 gastrectomy.[28]

The role of adjuvant radiotherapy in gastric cancer has become increasingly controversial given the results for both perioperative chemotherapy and, in patients undergoing D2 resection, postoperative adjuvant chemotherapy. The role of postoperative bolus 5-FU and folinic acid given in conjunction with postoperative radiotherapy after gastric cancer resection was first reported in 2001 in the Intergroup 0116 (SWOG 9008) trial.[29] Following gastric resection, patients were either observed or treated with 5-FU and folinic acid for 3 months, with administration during months 2 to 3 of 45 Gy of radiation therapy combined with 5-FU and folinic acid during weeks 1 and 5 of radiotherapy. Among the 556 patients treated, adjuvant therapy increased the 3-year overall survival from 41% to 50%. At long-term follow-up, a survival benefit of 10% was maintained for postoperative chemoradiotherapy.[30] However, when viewed in the context of more contemporary adjuvant therapy trials, the quality of surgical resection and lymph node retrieval was relatively poor in Intergroup 0116; only 10% of patients had a formal D2 resection, 36% had a D1 resection, and the majority (54%) had a D0 resection. Adjuvant therapy had no effect on reducing distant recurrence of disease, with the survival improvement due only to a reduction in local tumor recurrence with chemoradiotherapy.

The role of radiotherapy has now been evaluated in clinical trials in which more rigorous surgery was mandated as part of the protocol therapy. The ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial from Korea added radiation therapy to adjuvant chemotherapy after D2 resection.[31,32] Adjuvant chemotherapy with capecitabine and cisplatin was administered to 458 patients for six 3-week cycles, with or without 45 Gy of radiation therapy. The 5-year survival rates were similar for chemotherapy (73%) and chemoradiotherapy (75%). In a subset analysis, a small survival benefit was achieved with radiation therapy in patients who had node-positive intestinal cancers, and the subsequent ARTIST II trial (Phase III Randomized Trial of Adjuvant Chemotherapy With S-1 vs S-1/Oxaliplatin ± Radiotherapy for Completely Resected Gastric Adenocarcinoma; NCT01761461) is now comparing adjuvant chemotherapy with chemoradiotherapy in node-positive intestinal cancers.

Results of the CRITICS (Chemoradiotherapy After Induction Chemotherapy in Cancer of the Stomach) trial from the Netherlands, which have been reported but not published,[33] also address the contribution of postoperative radiation therapy after D1 or D2 resection in gastric cancer. Preoperative chemotherapy with 3 cycles of epirubicin, cisplatin, and capecitabine (ECC) followed by surgery was planned for all patients. After surgery, patients either completed 3 additional cycles of ECC or were treated with 45 Gy of radiotherapy combined with capecitabine and cisplatin. There was no difference between the postoperative radiotherapy and nonradiotherapy groups in median overall survival (3.3 and 3.5 years) or 5-year survival (41% for both).

Given these results, postoperative radiation therapy may be considered primarily in patients with gastric cancer undergoing less than a D1 resection. Chemotherapy

alone, given either perioperatively or postoperatively, is a validated therapeutic option in patients undergoing D1 or D2 resection.

Recurrence patterns as a function of the surgery performed in these adjuvant trials may also clarify the contribution of postoperative radiation therapy. The Intergroup 0116 trial (10% D2 resection rate) reported local recurrence as the first site of relapse in 29% of patients undergoing surgery alone, which was reduced to 19% with the addition of chemoradiotherapy. The MAGIC trial (42% D2 resection rate) reported local recurrence with surgery in 20% of patients, which was reduced to 14% with the addition of chemotherapy. In the ACTGS study (100% D2 resection rate), local recurrence was reported in 3% of patients receiving surgery alone and in 2% of those receiving S-1 in addition to surgery. In the CLASSIC trial (100% D2 resection rate), local recurrence was 8.5% with surgery alone and was reduced to 4.4% with the addition of adjuvant chemotherapy. In the ARTIST trial (100% D2 resection rate), local recurrence developed in 13% of those in the chemotherapy arm vs 7% of those in the chemoradiotherapy arm. Local recurrence appears to be less common with D2 resection.

Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, and its incidence is projected to increase.[1] The dismal 5-year overall survival rate of 5% to 10% is attributable to the fact that only 20% of patients present with operable disease, and of these, only 10% to 20% achieve long-term survival. The complex anatomy of the pancreas in relation to adjacent organs and vasculature, particularly when tumors occur in the head of the pancreas, raises the risk for locally inoperable disease. In addition, the aggressive nature of the disease leads to early metastasis.

Adjuvant therapy trials involving chemotherapy and radiation therapy are outlined in Table 3. A potential benefit of postoperative adjuvant chemotherapy and radiation therapy was suggested by the GITSG (Gastrointestinal Study Group) trial, which was reported in 1985.[34] After resection of pancreatic cancer with curative intent, 49 patients were randomly assigned either to observation or to adjuvant therapy with bolus 5-FU given during 2 weeks of a split course of 40 Gy of radiation therapy, followed by 2 years of weekly 5-FU. Survival at 5 years was 18% with chemoradiotherapy vs 8% with observation. The findings of this underpowered trial formed the basis for using postoperative 5-FU and radiation therapy over the ensuing decades. An attempt to reproduce these early results was undertaken by the European Organisation for Research and Treatment of Cancer (EORTC) in trial 40891, which was first reported in 1999[35] and updated with long-term follow-up in 2007.[36] EORTC 40891 randomly assigned 218 patients after surgery for pancreatic or periampullary adenocarcinoma either to observation or to a split course of 40 Gy of radiation therapy and 5-FU given by continuous infusion during the period of radiotherapy only. Nearly half of the patients treated had nonpancreatic primary tumors. A nonsignificant trend toward improved survival in the patients treated with adjuvant chemoradiotherapy who had pancreatic primary tumors continued to be nonsignificant in subsequent follow-up, with a median survival of 1 year in the observation arm and of 1.3 years in the treatment arm and no difference in long-term survival with or without treatment (hazard ratio [HR], 0.76; 95% CI, 0.52-1.12).

In 2001, the European Study Group for Pancreatic Cancer (ESPAC) reported the results from ESPAC-1,[37] a randomized trial in 541 patients with resected pancreatic cancer that compared observation alone with adjuvant chemotherapy, adjuvant chemoradiotherapy, or both. The statistical design was complex, with 285 patients randomly assigned in a 2 × 2 factorial design to chemotherapy, chemoradiation therapy, both, or observation; a further 68 patients were randomly assigned to chemoradiotherapy or no chemoradiotherapy, and 188 patients were randomly assigned to chemotherapy or no chemotherapy. Radiation therapy was administered to a total dose of 40 Gy in a split course of two 2-week treatments. Chemotherapy during radiation consisted of bolus 5-FU during the first 3 days of the first and second courses of radiotherapy, and adjuvant chemotherapy consisted of bolus 5-FU and folinic acid administered daily for 5 days, once every 4 weeks, for 6 cycles. In this trial, 19% of patients had positive surgical resection margins and 53% had node-positive disease. Among the 353 patients randomly assigned to chemoradiotherapy or no chemoradiotherapy, there was no survival difference (median survival, 15.5 and 16.1 months, respectively; P=.24). Among the 285 patients randomly assigned in the 2 × 2 factorial design, there was also no difference in median survival for chemoradiotherapy vs no chemoradiotherapy (15.8 vs 17.8 months; HR, 1.3). Among the 473 patients randomly assigned to chemotherapy vs no chemotherapy, there was a significant difference in median survival (19.7 vs 14.0 months; HR, 0.66). For the 285 patients randomly assigned in the 2 × 2 factorial design, a nonsignificant survival trend favoring chemotherapy was observed (17.4 vs 15.9 months; HR, 0.82). The authors concluded that further study of adjuvant chemotherapy was required, and that the inclusion of adjuvant radiation therapy as part of treatment might have a negative effect on survival.

Because of the unconventional design of ESPAC-1, the adoption of adjuvant chemotherapy alone without

Table 3. Trials of Adjuvant Therapy With or Without Radiation Therapy in Pancreatic Cancer

Trial	N	Treatment	Median Survival	5-y OS Rate
GITSG[34]	21	RT + 5-FU	20 mo	18%
	22	Surgery alone	11 mo	8%
EORTC 40891[35,36]	110	RT + 5-FU	1.3 y	HR 0.76, not SS
	108	Surgery alone	1.0 y	
ESPAC-1[37]	238	5-FU	19.7 mo	NS
	235	No 5-FU	14.0 mo	NS
CONKO-001[38,39]	179	Gemcitabine	22.8 mo	12.7%
	175	Surgery alone	20.2 mo	7.7%
RTOG 9704[40]	221	Gemcitabine + 5-FU/RT	20.5 mo	22%
	230	5-FU + 5-FU/RT	17.1 mo	18%
ESPAC-3[41]	537	Gemcitabine	23.6 mo	2-y, 49.1%
	551	5-FU	23.0 mo	2-y, 48.1%
ESPAC-4[43]	361	Gemcitabine + Capecitabine	28.0 mo	28.8%
	361	Gemcitabine	25.5 mo	16.3%

5-FU, 5-fluorouracil; mo, months; NS, not stated; OS, overall survival; RT, radiation therapy; SS, statistically significant; y, year.

radiation therapy was controversial until the results of the Charité Onkologie trial (CONKO-001) were reported in 2007 and updated in 2013.[38,39] In this trial, 354 patients who had undergone resection of pancreatic cancer were assigned either to no further therapy or to 6 months of adjuvant weekly gemcitabine given for 3 of every 4 weeks. More than 80% of the enrolled patients had negative margin resections, and 70% to 71% had node-positive disease. At early reporting, median disease-free survival improved from 6.7 to 13.4 months with adjuvant gemcitabine (P<.001), which achieved significance for the primary endpoint of the trial. At long-term follow-up, adjuvant gemcitabine doubled the 5-year overall survival rate from 10.4% to 20.7%. An increase in 10-year overall survival also was observed (12.2% vs 7.7%). A benefit for treatment was seen across all subgroups, including T stage, nodal status, and margin resection status. Although the difference in median survival was small for adjuvant gemcitabine vs observation (22.8 vs 20.2 months), the survival curves separated late, and the difference was significant (HR, 0.76; P=.01). The robust findings from this trial established the use of 6 months of postoperative gemcitabine without radiation therapy as a standard of care after pancreatic cancer resection.

Subsequently reported trials from the United States and Europe explored the benefits of adjuvant 5-FU vs gemcitabine, with or without the inclusion of radiation therapy. The US Intergroup/RTOG 9704 phase 3 trial studied 5-FU–based chemoradiation combined either with gemcitabine or with 5-FU chemotherapy after surgery.[40] All patients treated in this trial received 50.4 Gy of postoperative radiation therapy combined with a daily continuous infusion of 5-FU. Patients were randomly assigned either to receive gemcitabine weekly for 3 weeks before radiotherapy and 12 weeks after radiotherapy or to receive infusional 5-FU during the same treatment period. Nearly two-thirds of the patients treated had node-positive disease, and more than half of them had either a positive-margin surgical resection (33%-35%) or an unknown surgical resection margin status (23%-26%). When the patients treated with gemcitabine were compared with those treated with 5-FU, no difference was found in either median survival (20.5 vs 17.1 months, respectively) or the 5-year overall survival rate (22% vs 18%, respectively). A nonsignificant trend toward improved survival favoring gemcitabine was observed in patients with tumors of the pancreatic head, however (P=.08). In contrast to other trials, patients with elevated CA 19-9 levels were eligible for the trial. CA 19-9 values greater than 90 U/mL were found in 21% of the patients, suggesting persistent disease in these patients after surgical resection.

A similar survival equivalence for gemcitabine vs 5-FU as adjuvant therapy was reported in the ESPAC-3 trial.[41] This trial, which enrolled more than 1000 patients, compared the administration of 5-FU and folinic acid on days 1 to 5 of every 28 days for 6 cycles vs the weekly administration of gemcitabine during 3 of every 4 weeks for 6 cycles. More than 70% of patients had node-positive disease, and 35% had positive surgical resection margins. Median survival times were identical for 5-FU

(23.0 months) and gemcitabine (23.6 months; HR, 0.94; *P*=.39), as were the 2-year survival rates (48.1% and 49.1%, respectively). More cases of stomatitis and diarrhea were seen in the 5-FU arm, and more cases of hematologic toxicity in the gemcitabine arm. The results from ESPAC-3 reinforced a survival benefit for adjuvant chemotherapy after resection of pancreatic cancer and indicated that either 5-FU or gemcitabine is an appropriate therapy.

In contrast to Western trial results, which suggested parity for adjuvant fluorinated pyrimidine chemotherapy vs gemcitabine, a recent trial conducted in Japan suggested superiority for the oral fluorinated pyrimidine S-1 compared with gemcitabine.[42] In this trial, 385 patients received either 6 months of weekly gemcitabine or S-1 adjuvant chemotherapy. The majority of patients had node-positive disease (62%-64%) and a negative-margin resection (86%-88%). The HR for risk for death strongly favored the S-1 arm (HR, 0.57; *P*<.0001), with a significant improvement in median survival for S-1 vs gemcitabine (46.5 vs 25.5 months, respectively) as well as in relapse-free survival (22.9 vs 11.3 months, respectively). The results from this trial are provocative but require confirmation given the surprising magnitude of the difference seen between the treatment arms.

A potential new care standard in the West was established with report of the ESPAC-4 trial.[43] In this trial, 722 patients were randomly assigned after resection either to weekly gemcitabine or to weekly gemcitabine combined with oral capecitabine for 6 months. The majority of patients had node-positive disease (80%) and a positive-margin resection (60%). Median survival was improved for combination therapy (28.0 months) vs single-agent therapy (25.5 months; HR, 0.82; *P*=.032), with encouraging 5-year overall survival for the combination therapy group (28.8%) vs the single-agent therapy group (16.3%).

Collectively, contemporary randomized trials of adjuvant therapy in pancreatic cancer support a survival benefit from the use of adjuvant chemotherapy with either gemcitabine or 5-FU, and a potentially optimal benefit from therapy combining gemcitabine and capecitabine after surgery. Notwithstanding the caveats regarding cross-trial comparisons, median and overall survival results appear to be similar for modern trials whether or not adjuvant radiotherapy was given postoperatively. Survival benefits for adjuvant chemotherapy, even in patients with positive surgical margins, further question the contribution of radiation therapy after pancreatic cancer resection. The study of newer-generation regimens as adjuvant therapy in pancreatic cancer, including the combination of gemcitabine and nab-paclitaxel (Abraxane, Celgene; NCT01964430) and the combination of folinic acid, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX; NCT01526135) is ongoing. The ongoing RTOG 0848 trial is comparing adjuvant chemotherapy with gemcitabine with or without the addition of postoperative radiotherapy after pancreatic cancer resection (NCT01013649). In this trial, patients must first complete 5 months of adjuvant chemotherapy before randomization either to continue adjuvant chemotherapy or to receive capecitabine and radiotherapy to complete adjuvant therapy. The delay in radiation therapy could select out patients with early recurrence of metastatic disease and might enhance the benefit of adjuvant radiotherapy.

The current standards of care after pancreatic cancer resection include adjuvant chemotherapy alone and chemotherapy plus radiation therapy. Results to date, however, are not compelling enough to mandate the inclusion of radiotherapy as part of adjuvant management. The results of RTOG 0848 are eagerly awaited.

The role of radiation therapy has also been explored in patients with locally advanced and unresectable pancreatic cancer. Mixed results were seen in underpowered randomized trials and in some retrospective series suggesting an uncertain benefit from adding radiation therapy to chemotherapy in unresectable disease. A salient negative randomized trial called LAP07 (Randomized Multicenter Phase III Study in Patients With Locally Advanced Adenocarcinoma of the Pancreas: Gemcitabine With or Without Chemoradiotherapy and With or Without Erlotinib) showing failure of radiotherapy to improve outcome in locally advanced disease was recently reported.[44] In this international multicenter trial, patients with locally advanced, unresectable pancreatic cancer received chemotherapy weekly with gemcitabine, with or without the anti-EGFR agent erlotinib (Tarceva, Genentech/Astellas), for 4 months. Patients with a response or stable disease and in whom distant metastatic disease did not develop were then randomly assigned to continue chemotherapy or to receive chemoradiotherapy in which 54 Gy of radiation was given concurrently with capecitabine. Of 442 patients receiving induction chemotherapy, 269 (61%) underwent randomization to receive or not receive radiation therapy. Of these patients, nearly two-thirds had primary tumors in the pancreatic head, one-third had body and tail lesions, and 40% to 42% had clinical evidence of disease in regional lymph nodes. The median survival times of patients treated with (15.2 months) or without radiation therapy (16.5 months) did not differ (HR, 1.03; *P*=.83). Locoregional progression was less common in the radiotherapy group (32%) vs the chemotherapy group (46%), whereas metastatic progression was more common in the radiotherapy arm (60%) compared with the chemotherapy arm (44%). The addition of erlotinib to chemotherapy had no beneficial effect in any treatment group.

Interest in the potential role of radiation therapy in unresectable or borderline resectable pancreatic cancer has

been renewed with the use of stereotactic body radiation therapy, which delivers high-dose fraction radiotherapy over 5 days. Recent studies suggest that this approach is feasible and tolerable,[45] and further study is ongoing.

Cholangiocarcinoma and Biliary Cancer

Cancers of the biliary tree and gallbladder are relatively uncommon in the United States and account for fewer than 1% of cancer cases and cancer-related deaths.[1] Evidence for the use of adjuvant chemotherapy or radiation therapy comes largely from retrospective studies and limited prospective series, which often have reached divergent conclusions about the benefits of such therapy. The protracted time frame over which such cases are sampled, the heterogeneity of the surgery performed and margin status achieved, the lack of a standardized chemotherapy regimen, the potential for selection bias for patients treated vs those not treated, and the frequent admixture of treated patients with pancreatic, ampullary, and duodenal cancers are only some of the issues limiting interpretation of these studies. Despite the potential for surgical cure, patients run a substantial risk for both local tumor recurrence and systemic dissemination of disease.

Although consensus has emerged that cisplatin plus gemcitabine is the optimal chemotherapy to treat metastatic biliary cancer and cholangiocarcinoma,[46] data for the use of adjuvant chemotherapy are largely limited to uncontrolled retrospective studies. One randomized trial from Japan of observation vs adjuvant chemotherapy, which studied a combination of mitomycin and 5-FU, treated various primary tumor sites and enrolled patients with both curative and positive resection margins. An observation of a 5-year survival benefit for adjuvant chemotherapy in patients with primary tumors of the gallbladder lost statistical significance when an intent-to-treat analysis was applied.[47] The ESPAC group performed a prospective randomized trial comparing adjuvant chemotherapy with either 5-FU/folinic acid or gemcitabine vs observation after curative surgery in 434 patients with cancers of the ampulla, duodenum, or intrapancreatic biliary duct, clearly a heterogeneous population.[48] The majority had node-positive disease (54%-62%) and R0 resections (81%-86%). Chemotherapy consisted of folinic acid plus 5-FU for 5 days every month or gemcitabine once a week for 3 of 4 weeks each month, for 6 monthly cycles. No significant difference in median survival was observed between the 2 chemotherapy groups (43.1 months) and the observation group (35.2 months; HR, 0.86; P=.25). After adjustment for prognostic variables, however, adjuvant chemotherapy conveyed a survival benefit, with a reduction in risk for death of 25% (HR, 0.75; P=.03), with similar benefits for 5-FU (HR, 0.75) and gemcitabine (HR, 0.70). Collectively, the data supply supportive but nondefinitive evidence of a benefit of adjuvant chemotherapy in biliary cancer and cholangiocarcinoma.

Assessment of a role for postoperative radiation therapy in biliary cancer and cholangiocarcinoma is also largely limited to retrospective series. Some of the largest of these come from reviews of the Surveillance, Epidemiology, and End Results (SEER) Program database. One review assessed more than 5000 patients with intrahepatic cholangiocarcinoma undergoing limited or radical surgery; some patients received postoperative radiation therapy, with no documentation of whether chemotherapy was also administered.[49] An early survival benefit at 1 year favoring radiation therapy was lost at 5-year follow-up. To overcome imbalances in prognostic features between the group receiving and the group not receiving radiotherapy, a propensity-matched survival analysis was performed and indicated a median survival improvement from 11 to 18 months when radiation therapy was added to surgery (HR, 0.45; P<.001). A SEER database review of more than 4000 patients with gallbladder cancer treated with surgery with or without radiation therapy has also been reported, but again information regarding the use of chemotherapy is not available.[50] Overall survival appeared to improve with the inclusion of radiation therapy (15 vs 8 months; P<.0001), with multivariate regression analysis suggesting a benefit in stage T2 or higher or node-positive tumors. The absence of information about the concomitant use of chemotherapy in these series limits interpretation of the results.

Because of the potential for concurrent chemotherapy to enhance radiation therapy effectiveness while also delivering active systemic therapy, adjuvant radiation therapy is usually given with chemotherapy. A SEER-Medicare database review assessed more than 1000 patients treated with surgery alone, adjuvant chemotherapy, or adjuvant chemoradiotherapy for resected gallbladder cancer.[51] A survival improvement was observed for both adjuvant chemotherapy (P=.034) and chemoradiotherapy (P<.001). A 2012 meta-analysis of adjuvant therapy in biliary tract cancer involved more than 6700 patients and 20 studies,[52] nearly all of which were retrospective patient reviews. A survival benefit was suggested for adjuvant chemotherapy (odds ratio [OR], 0.39; P<.001) and chemoradiotherapy (OR, 0.61; P=.049) compared with radiotherapy alone (OR, 0.98; P=.90). Patients with node-positive disease appeared to derive the greatest benefit from adjuvant therapy, and patients with either R0 or R1 resections also appeared to benefit. A benefit for adjuvant radiation therapy, however, was lost in patients achieving clear surgical margins (OR, 1.26; P=.20).

Outcome and failure pattern may also vary according to the primary site of the cancer. A recent retrospective

review of 177 patients treated at a single institution with surgery alone indicated a higher rate of isolated locoregional recurrence in hilar cholangiocarcinoma (59%) than in gallbladder cancer (15%), with a greater tendency for the early development of distant metastatic disease in cholangiocarcinoma. These findings suggest a potentially greater role for the use of adjuvant radiotherapy in hilar cholangiocarcinoma.[53] The Southwest Oncology Group recently reported a 70-patient pilot trial of adjuvant chemotherapy with capecitabine and gemcitabine followed by radiation therapy and capecitabine in patients with resected extrahepatic cholangiocarcinoma and gallbladder cancer.[54] Rates of overall survival and distant and local recurrence were encouraging, and this trial has stimulated ongoing interest in a trial of adjuvant therapy in this disease.

US treatment recommendations, reflected in the National Comprehensive Cancer Network (NCCN) Guidelines, reflect the results reported in these largely retrospective series.[55] The guidelines include recommendations to consider observation alone or adjuvant chemotherapy with a fluorinated pyrimidine or gemcitabine for resected gallbladder cancer, and fluorinated pyrimidine–based chemoradiation therapy for patients with stage T2 or higher or node-positive disease or with R1 resection. For intrahepatic cholangiocarcinoma, observation alone after R0 resection is recommended, as well as consideration of adjuvant chemotherapy with a fluorinated pyrimidine or gemcitabine. Fluorinated pyrimidine–based chemoradiation is recommended after R1 resection or for node-positive disease. For extrahepatic cholangiocarcinoma, recommendations include observation, adjuvant chemotherapy, or chemoradiotherapy after either R0 or R1 resection.

New Directions

The success of combined-modality approaches incorporating radiation therapy, chemotherapy, and surgery has been modest at best in treating UGI cancers. A greater understanding of the biology of these diseases will likely emerge with the publication of genomic profiling data for these cancers, exemplified by The Cancer Genome Atlas project. Molecular subtyping of these cancers may lead to the ability to tailor therapies based on molecular profiling, including the identification of targetable tumor growth pathways and pathways leading to an enhanced response to therapy or to resistance. Novel radiotherapy approaches, including intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy, and proton-based radiotherapy, are the subject of ongoing investigation. The inclusion of immune checkpoint inhibitors in combined-modality therapy is also an area of emerging investigation.

Conclusions

Radiation therapy plays an integral part of the management of UGI cancers. For esophageal cancer, primary chemoradiotherapy or chemoradiotherapy followed by surgery is an established standard of care. For gastric cancer, postoperative radiation therapy appears necessary when surgical resection is potentially inadequate but may not be required after resection in all patients. The role of radiation therapy in the management of pancreatic cancer currently remains uncertain in both the adjuvant setting and the setting of locally unresectable disease. Radiation therapy for biliary cancers also does not have a clearly defined role, although treatment guidelines consider the use of radiation therapy combined with chemotherapy in node-positive or disease with positive margins after resection.

Disclosures

Dr Ilson has been a consultant for or served on the advisory boards of Amgen, Merck, AstraZeneca, Eli Lilly/ImClone, Macrogenics, Bayer, Pieris, Genentech/Roche, and Bristol-Myers Squibb.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917.
3. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Br J Surg*. 1980;67(6):381-390.
4. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.
5. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol*. 2012;19(1):68-74.
6. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med*. 1998;339(27):1979-1984.
7. Medical Research Council Esophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in esophageal cancer: a randomized controlled trial. *Lancet*. 2003;359:1727-1733.
8. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol*. 2009;27(30):5062-5067.
9. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715-1721.
10. Alderson D, Langley RE, Nankivell MG et al. Neoadjuvant chemotherapy for resectable esophageal and junctional adenocarcinoma: results of the UK Medical Research Council randomized OEO5 trial [ASCO abstract 4002]. *J Clin Oncol*. 2015;3315)(suppl).
11. Cunningham D, Smyth E, Stenning S et al. Peri-operative chemotherapy +/- bevacizumab for resectable gastro-oesophageal adenocarcinoma: results from the UK Medical Research Council randomized STO3 trial [ECC abstract 2201]. *Eur J Cancer*. 2015;51(3)(suppl).
12. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992;326(24):1593-1598.
13. Cooper JS, Guo MD, Herskovic A, et al; Radiation Therapy Oncology Group.

Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA*. 1999;281(17):1623-1627.
14. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol*. 2005;23(10):2310-2317.
15. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol*. 2007;25(10):1160-1168.
16. Ajani JA, D'Amico TA, Almhanna K, et al; National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Canc Netw*. 2015;13(2):194-227.
17. van Hagen P, Hulshof MC, van Lanschot JJ, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074-2084.
18. Shapiro J, van Lanschot JJ, Hulshof MCCM, et al; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16(9):1090-1098.
19. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol*. 2013;24(11):2844-2849.
20. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. *Lancet Oncol*. 2013;14(7):627-637.
21. Ilson DH, Moughan J, Suntharalingam M, et al. RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery [ASCO abstract 4007]. *J Clin Oncol*. 2014;32(5)(suppl).
22. Bendell JC, Meluch A, Peyton J, et al. A phase II trial of preoperative concurrent chemotherapy/radiation therapy plus bevacizumab/erlotinib in the treatment of localized esophageal cancer. *Clin Adv Hematol Oncol*. 2012;10(7):430-437.
23. Fitzmaurice C, Dicker D, Pain A, et al; Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505-527.
24. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up of the randomized nationwide Dutch D1D2 trial. *Lancet Oncol*. 2010;11(5):439-449.
25. Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
26. Sasako M, Sakuramoto S, Katai H, et al. 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. *J Clin Oncol*. 2011;29(33):4387-4393.
27. Noh SH, Park SY, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 resection (CLASSIC): 5-year follow up of an open-label, randomized phase III trial. *Lancet Oncol*. 2014;15(12):1389-1396.
28. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(10):1286-1312.
29. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345(10):725-730.
30. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012;30(19):2327-2333.
31. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capeciradiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST Trial. *J Clin Oncol*. 2012;30(3):268-273.
32. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, including survival and subset analysis. *J Clin Oncol*. 2015;33(28):3130-3136.
33. Verheij M, Jansen EP, Annemieke C, et al. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: first results from the CRITICS Study [ASCO abstract 4000]. *J Clin Oncol*. 2016;34(15)(suppl).
34. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987;59(12):2006-2010.
35. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Ann Surg*. 1999;230(6):776-782.
36. Smeenk HG, van Eijck CHJ, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg*. 2007;246(5):734-740.
37. Neoptolemos JP, Dunn JA, Stocken DD, et al; European Study Group for Pancreatic Cancer. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358(9293):1576-1585.
38. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer a randomized controlled trial. *JAMA*. 2007;297(3):267-277.
39. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013;310(14):1473-1481.
40. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. 2011;18(5):1319-1326.
41. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection a randomized controlled trial. *JAMA*. 2010;304:1073-1081.
42. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). *Lancet*. 2016;388(10041):248-257.
43. Neoptolemos JP, Palmer D, Ghaneh P, et al. ESPAC-4: A multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP) versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma [ASCO abstract LBA4006]. *J Clin Oncol*. 2016;34(15)(suppl).
44. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib the LAP07 randomized clinical trial. *JAMA*. 2016;315(17):1844-1853.
45. Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys*. 2017;97(2):313-322.
46. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281.
47. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer*. 2002;95(8):1685-1695.
48. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA*. 2012;308(2):147-156.
49. Hyder O, Dodson RM, Sachs T, et al. Impact of adjuvant external beam radiotherapy on survival in surgically resected gallbladder adenocarcinoma: a propensity score-matched Surveillance, Epidemiology, and End Results analysis. *Surgery*. 2014;155(1):85-93.
50. Wang SJ, Fuller CD, Kim JS, Sittig DF, Thomas CR Jr, Ravdin PM. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. *J Clin Oncol*. 2008;26(13):2112-2117.
51. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol*. 2011;29(35):4627-4632.
52. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2012;30(16):1934-1940.
53. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder cancer and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer*. 2003;98(8):1689-1700.
54. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG 0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. *J Clin Oncol*. 2015;33(24):2617-2622.
55. Benson AB III, D'Angelica MI, Abrams TA, et al. Hepatobiliary cancers, version 2.2014. *J Natl Compr Canc Netw*. 2014;12(8):1152-1182.