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Drug Delivery Opportunities in Esophageal Cancer: Current Treatments and Future Prospects

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Abstract

With one of the highest mortality rates of all malignancies, the 5-year survival rate for esophageal cancer is under 20%. Depending on the stage and extent of the disease, the current standard of care treatment paradigm includes chemotherapy or chemoradiotherapy followed by surgical esophagogastrectomy, with consideration for adjuvant immunotherapy for residual disease. This regimen has high morbidity, due to anatomic changes inherent in surgery, the acuity of surgical complications, and off-target effects of systemic chemotherapy and immunotherapy. We begin with a review of current treatments, then discuss new and emerging targets for therapies and advanced drug delivery systems. Recent and ongoing pre-clinical and early clinical studies are evaluating traditional tumor targets (e.g., human epidermal growth factor receptor 2), as well as promising new targets such as Yes-associated protein 1 or mammalian target of rapamycin to develop new treatments for this disease. Due the function and location of the esophagus, opportunities also exist to pair these treatments with a drug delivery strategy to increase tumor targeting, bioavailability, and intratumor concentrations, with the two most common delivery

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Patient with esophageal cancer have the highest mortality rates of all cancer malignancies. A team led by surgeon, Dr. Uma Sachdeva, a surgeon and chemist/bioengineer, Dr. Grinstaff, review the latest surgical and pharmacological treatments for esophageal cancer and discuss new and emerging targets for therapies and advanced drug delivery systems.

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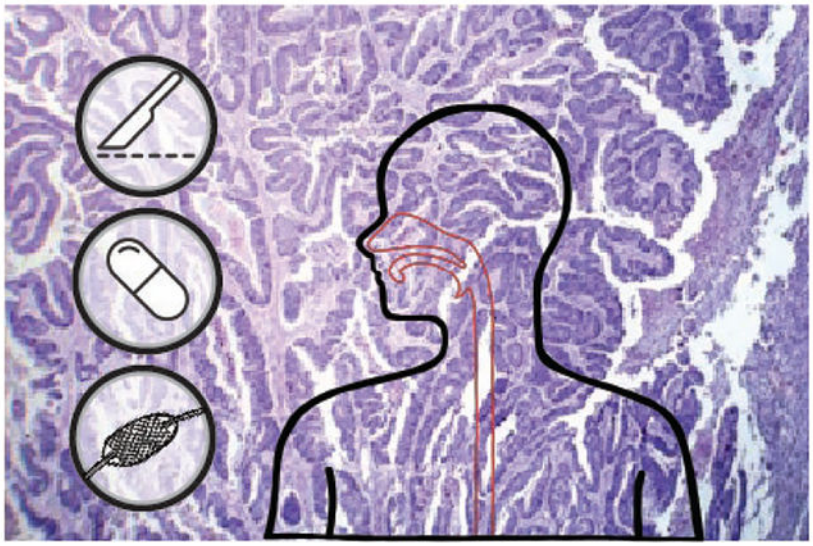
platforms being stents and nanoparticles. Finally, early results with antibody drug conjugates and chimeric antigenic receptor T cells also show promise as upcoming therapies. This review discusses these innovations in therapeutics and drug delivery in the context of their successes and failures, with the goal of identifying those solutions that demonstrate the most promise to shift the paradigm in treating this deadly disease.

Graphical Abstract



Keywords

esophageal cancer; drug delivery; immunotherapy; nanoparticles; stents; antibody-drug conjugates

Introduction

Esophageal cancer is the sixth most common cause of cancer deaths worldwide, with a 20% 5-year survival rate[1]. Its prevalence in Western countries has increased 6-fold over the past 20 years, associated with increasing rates of obesity and gastroesophageal reflux disease[2,3]. There are two major subtypes of esophageal cancer: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC is the most common type of esophageal cancer in the United States and Western Europe and primarily affects Caucasian males. EAC is associated with Barrett's esophagus - intestinal metaplasia of the normal squamous esophageal mucosal epithelium, which results from acid or bile reflux associated with chronic gastroesophageal reflux disease. Globally, however, ESCC is the most common type of esophageal cancer, accounting for 87% of cases worldwide[4]. Risk factors for development of ESCC include use of alcohol or tobacco and dietary intake of nitrites and hot temperature liquids. The role of environmental factors, including diet and lifestyle, in disease prevalence is supported by the lower rate of ESCC in Chinese immigrants in the US as compared to those living in China[5]. While the incidence of ESCC in the Western world (North America, Western Europe, and Australia) is declining, rates of EAC continue to increase. In the USA alone, the incidence escalated from 0.4 to 2.8 per 100,000 people between 1973 and 2012[4].

Of all major cancers, esophageal cancer exhibits one of the lowest overall survival rates, with the best predictive measure of survival being tumor stage or extent of disease at the time of clinical presentation. Although overall survival is only 20%, survival rates can increase up to 50% in the setting of localized disease, and up to 70% for superficial tumors limited to the esophageal mucosa[6]. The current clinical standard consists of chemotherapy or chemoradiotherapy, followed by esophagogastrecomy, with consideration for adjuvant immunotherapy for residual disease[7]. Esophagogastrectomy is a complex procedure requiring mobilization and resection of the thoracic and intra-abdominal esophagus and proximal stomach, tubularization of the remaining stomach, and anatomic reconstruction via esophagogastric anastomosis. This operation bears a 10–30% risk of anastomotic leak, which in turn can lead to delayed stricture formation, severe mediastinitis, empyema, sepsis, respiratory complications, and even death. Other common complications include atrial dysrhythmia and pneumonia, and postoperatively all patients endure significant changes to their quality of life resulting from this anatomic reconstruction[8].

Neoadjuvant therapy includes chemotherapy and radiation for ESCC and chemotherapy with or without radiation for EAC and has demonstrated a clear survival benefit for locally advanced disease in multiple studies[9–12]. However, systemic chemotherapy is associated with significant side effects and toxicities, including fatigue, hair loss, nausea, weight loss, neutropenia, and neuropathy[13], further decreasing patients' quality of life. In this review, we summarize the challenges associated with current treatment options and discuss novel targeted therapies and chemotherapy delivery platforms. Specifically, we examine: 1) traditional anticancer targets which are only recently being explored in the setting of esophageal cancer, such as HER2 and VEGF; 2) targeted therapies related to esophageal and gastric cancers, such as CLDN18.2; and, 3) novel pathways that are emerging from ongoing research, including Yes-associated protein 1 (YAP1). This review then examines evolving drug delivery platforms for this disease, including drug-impregnated esophageal stents and loaded nanoparticles, and comments on the future of drug delivery, such as antibody-drug conjugates. The purpose of this review is to stimulate discussions, highlight clinical approaches and successes over the past decade, and provide further motivation to develop more effective treatment options for this deadly disease.

Esophageal Cancer Treatments in the Clinic

Current treatment options for esophageal cancer depend on histologic subtype, tumor location, and tumor stage. Radial penetration depth, dissemination to regional lymph nodes, and distant spread to lymph nodes or other organs defines the American Joint Committee on Cancer (AJCC) staging system (0-IV) for EC (Figure 1[14]). This section details current treatment approaches, highlights associated challenges, and reviews newer strategies currently undergoing clinical and preclinical evaluation.

Endoscopic Therapy

Patients with small, superficial tumors (stage 0 or I) are candidates for organ-preserving procedures via endoscopic resection strategies. Tumors limited to the mucosa with no invasion into the submucosal layer (T1a) and no suspected lymph node involvement are

resected by endoscopic mucosal resection (EMR). This technique partially aspirates the lesion into a specialized cap placed on the tip of the endoscope or bands it at the base, and then resects the lesion using a cauterizing snare[15]. Traditional criteria for EMR with curative intent include well-differentiated tumors (<2 cm) lacking lymphovascular invasion, in which a negative margin can be achieved endoscopically. The two forms of EMR include cap-assisted EMR and band-assisted EMR. Band-assisted mucosectomy is more efficient for larger lesions, with similar success rates for smaller lesions (<15 mm) relative to cap-assisted EMR, and both are associated with fewer complications compared to traditional surgical resection[16]. Using these techniques, curative resections can be achieved for both adenocarcinoma and squamous cell carcinoma.

Endoscopic submucosal dissection (ESD) is a more complex resection technique that targets tumors invading the superficial layer of the submucosa. Expanded criteria for ESD include tumors of any size, well or moderately differentiated, that lack lymphovascular invasion and invade <500 micrometers into the submucosa (SM1 by Paris classification), for which negative margin can be achieved endoscopically. The submucosa surrounding the lesion is injected multiple times with a viscous solvent to establish the submucosal plane, and then the lesion is dissected with a cauterizing knife. This technique requires more precision and technical skill than EMR, with a higher risk of complications including bleeding and full thickness perforation. However, ESD allows for greater resection area and offers more pathological information regarding margin status for larger lesions that would otherwise require resection via serial EMR[17] by allowing for a single specimen with anatomic orientation. A comparison of these two techniques, as reported by Takashi et al., shows similar overall survival due to development of distant metastasis, however cumulative disease-free survival was significantly greater with ESD than with EMR[18]. Data from a larger meta-analysis comparing the two techniques reveals that ESD provided significantly higher en bloc, curative, and R0 resection rates with lower local rates of recurrence, while having similar complication rates[19]. As these approaches become more widely adopted in Western countries, and further improvements are made in endoscopic tools and predictive modeling for lymph node metastasis, endoscopic resection techniques may become more widely applied to larger tumors without lymph node involvement to enable organ preservation and improved quality of life.

Surgery

For patients with larger tumors (stage II/III), resection requires surgical resection via partial or near-total esophagectomy with reconstruction, most commonly using a gastric conduit. Based on the location of the tumor, the surgeon within a multidisciplinary team setting determines the extent and approach to resection. Tumors in the distal third of the esophagus are typically resected via Ivor Lewis esophagogastrectomy, a 2-stage procedure under single anesthetic that involves mobilization of the distal esophagus and stomach followed by tubularization of the stomach to create the conduit that will be used as the “neo-esophagus” via an intra-abdominal approach. This is followed by dissection of the intrathoracic esophagus, resection and removal of the specimen, and intrathoracic anastomosis of the proximal *in situ* esophagus to the gastric conduit via a right sided transthoracic approach[20]. This procedure can be performed open or minimally invasively, via traditional laparoscopic

and thoracoscopic approaches or with robotic assistance. Clinical trials comparing the two techniques find that patients undergoing minimally invasive esophagectomy exhibit significantly fewer complications than those undergoing open surgical approach[21], with no difference in either disease-free or overall survival[22]. Mid-esophageal tumors are resected via McKeown, or 3-hole, esophagectomy involving transthoracic, transabdominal, and transcervical approaches. This procedure begins with mobilization of the intrathoracic esophagus via the right chest, followed by mobilization of the intrabdominal esophagus and stomach and gastric tubularization, followed by dissection of the proximal esophagus and anastomosis within the left neck to achieve appropriate margin. This procedure can also be performed via open or minimally invasive techniques[23]. The transhiatal approach to esophagectomy involves mobilization of the intrathoracic esophagus from a transabdominal approach by dissection into the mediastinum through the esophageal hiatus, followed by anastomosis in the left neck, and is typically used for earlier stage esophageal tumors given the limited intrathoracic lymph node dissection from this approach[24]. Resection of tumors located in the proximal third of the esophagus is more challenging and morbid due to proximity to the larynx and pharynx, and proximal tumors are therefore typically treated with definitive chemotherapy and radiation. Despite significant advances in surgical techniques including adoption of robotic surgical approaches, 5-year survival remains low[25], highlighting the need for additional treatment options.

Neoadjuvant Treatments for Resectable Disease

The overall 5-year survival for esophageal cancer remains poor due to development of distant metastatic disease[26]. Neoadjuvant treatment extends survival for patients with locally advanced esophageal cancer[27–29]. Clinical trials by the Japanese Clinical Oncology Group show that neoadjuvant chemotherapy or chemoradiation provides improved disease-free and overall survival rates, as well as prevention of relapse, compared to surgery alone for patients with ESCC.[30–32] Neoadjuvant chemoradiation is now standard for ESCC prior to surgery in both Japan and Western countries. Results of neoadjuvant chemoradiation are so effective for ESCC that ongoing trials are currently investigating the role for surgery versus clinical surveillance in patients who demonstrate complete clinical response following initial chemoradiation[33,34].

For EAC, debate continues regarding optimal neoadjuvant strategy, though standard of care at most centers includes neoadjuvant chemotherapy or chemoradiation followed by surgical resection. Several studies including the CROSS trial show a modest survival benefit for carboplatin/paclitaxel with radiation, however this survival benefit was less than that observed for ESCC[35]. Additional studies demonstrate the efficacy of combination chemotherapeutics in the perioperative setting, including docetaxel, carboplatin, and 5-fluorouracil. Clinical trial results comparing neoadjuvant chemoradiation versus perioperative chemotherapy show improvement over surgery alone, but do not demonstrate a significant difference in overall survival between these two approaches[36,37]. While most North American centers continue to use a neoadjuvant chemoradiation strategy for EAC, determination of an optimized chemoradiotherapy protocol requires additional studies as there are inconsistencies in prior clinical trials with radiation dosing[38,39],

chemotherapy regimen[40–42], and timing of surgical intervention[43–45]. Ongoing trials are also investigating the comparative efficacy of proton versus photon radiation approaches.

For patients with unresectable tumors due to local invasion into critical structures, proximal location, or inability to tolerate esophagectomy due to comorbidities or frailty, chemoradiation without surgery is the standard treatment approach. Ongoing clinical trials are investigating optimal chemotherapy and chemoradiation protocols in both EAC and ESCC, as well as the role for surgery in patients who demonstrate complete clinical response to neoadjuvant treatments[46–52], and the emerging role for neoadjuvant immunotherapy in resectable disease, as discussed in the next section.

Immunotherapy

Immunotherapy is one of the most exciting emerging fields in oncology at present. The first immunotherapy agent was approved by the FDA in 1986, however the field experienced exponential growth in the 2010s[53]. Pembrolizumab and nivolumab are IgG4 monoclonal antibodies that block programmed death-ligand 1 (PD-L1) to prevent immune evasion by cancer cells and are currently in use for treatment of several malignancies in the neaodjuvant, adjuvant, and advanced/metastatic settings, including both gastric and esophageal cancers[54]. PD-L targeting is prevalent within immunology, and expression of PDL-1 in tumors is prognostic for treatment response to PDL-1 or PD-1 inhibition, and, in some cases, is predictive of development of metastatic disease[55].

Currently, both pembrolizumab and nivolumab are approved for the treatment of esophageal cancer in combination therapies in the advanced and adjuvant settings, with ongoing trials of its role in the neoadjuvant setting. Results of the Checkmate 577 trial (Figure 2[56]) demonstrate that treatment with nivolumab after resection following neoadjuvant chemoradiotherapy increases average survival to 22.4 months, as compared to 11.0 months in the placebo group ($p= 0.0003$)[54]. The Checkmate 648[57] and ATTRACTION-3[58] trials further support this finding with similar results: nivolumab in conjunction with chemotherapy significantly prolongs survival in patients with advanced ESCC. These results motivate further investigation, and as a result there are approximately one hundred ongoing/recruiting clinical trials using immunotherapy for the treatment of esophageal cancer including both ESCC and EAC.

The use of newer investigational anti-PD-1 therapies and their efficacy relative to, or in addition to, chemotherapy are ongoing in the advanced/metastatic setting. These agents include camrelizumab[59,60], sintilimab[61,62], toripalimab[63], and tislelizumab[64], which show modest survial improvements in advanced disease in the first-or second-line settings. The use of combination ipilimumab, which targets CTLA-4, with nivolumab also improves survival relative to chemotherapy alone[65]. As the immunotherapy field continues to advance, we anticipate these newer anti PD-1, anti PD-L1, and anti CTLA-4 agents will begin to be used in the neoadjuvant and adjuvant settings for patients with locally advanced resectable disease. Novel approaches to immune modulating therapy, including CAR-T cells and adoptive cell therapies will be discussed further below.

Emerging Targets for Tumor Targeting

The clinical standard for chemotherapy administration is systemic delivery. Unfortunately, this delivery method affords only a fraction of the drug (<10%) reaching the disease site with greater levels of the drug reaching major organs such as the liver and kidneys[66]. To decrease the off-target toxicities of systemic delivery, new techniques are being explored to target the surface proteins of tumor cells using antibodies, peptides, and/or other proteins. This section details examples of traditionally used tumor targets, as well as promising newer strategies in preclinical development.

Genomics and molecular classification

One of the hallmarks of cancer is the dysregulation of genetic pathways associated with cell growth, proliferation, and neovascularization. ESCC and EAC possess unique genetic and genomic mutations, suggesting these two disease histologies may have separate origins. ESCC shows similarity to other head and neck cancers, with genomic amplifications of CCND1, SOX2, and TP63[67]. Meanwhile, EAC is more akin to gastric cancer, as both possess amplifications of VEGF, ERBB2, and GATA4[68]. These differences in mutational signatures suggest that ESCC and EAC may respond to more specific treatment strategies, with only limited overlap in their susceptibility to targeted agents.

ESCC and EAC do share one such common target: the receptor tyrosine kinase-ras-phosphatidylinositol-3-kinase (Ras/PI3K) pathway, which is dysregulated in 50–60% of ESCC and 60–75% of EAC[69]. In this pathway, ERBB2, VEGF, and KRAS gain-of-function mutations prevail, yet none are as highly expressed as EGFR, which is present in 30% of all EC (Figure 3[70]). EGFR is the second most frequent receptor tyrosine kinase alteration in EAC, behind KRAS, demonstrating chromosomal instability in 5–10% of tumors[71]. While targeting this pathway is conceptually promising, current trial results have yet to show benefit of EGFR inhibitors against metastasis.

ERBB2, EGFR, and KRAS amplifying mutations tend to be mutually exclusive. These genes possess a common downstream tumor promoting effect through the activity of cell cycle genes CCND1, CDK4, and CDK6. 67% of EAC and over 90% of ESCC contain alterations of the cell cycle pathway[72] and research into CDK4/6 inhibitors in the pre-clinical setting is a promising ongoing field of study.

ESCC also exhibits mutations in NOTCH1, PIK3CA, SOX2 and TP63 pathways, whereas EAC expresses elevated levels of PI3K/Akt and mTOR, all associated with tumor progression and drug resistance[73,74]. Such molecular pathway discoveries are informing and enabling researchers to selectively target tumor cells by histologic subtype, while mitigating off-target drug effects. Below, we further detail several of these pathways and the ongoing work both clinically and in preclinical development.

Human epidermal growth factor receptor 2 (HER2)—Human epidermal growth factor receptor 2 (HER2) is a highly targeted receptor across several cancers and historically most associates with breast cancer phenotypes; however, this receptor is also present in ovarian, gastric, and esophageal cancers (Figure 3[70]). The HER2 proto-oncogene encodes a

185 kDa transmembrane glycoprotein receptor with intracellular tyrosine kinase activity[75]. Both EAC and ESCC upregulate HER2 in ~15% of cases[76]. In gastric cancers, up to 25% show HER2 overexpression, although the prognostic value remains unclear[77]. HER2 overexpression in gastric/esophageal cancer coincides with a higher incidence of heterogeneity (focal staining) than breast cancer[78], limiting the predictive value[79].

There are currently several HER2-targeted therapies approved in the clinic for the treatment of esophageal cancer, most notably trastuzumab - a HER2-targeted humanized monoclonal antibody. In 2010, the FDA approved trastuzumab following the success of the ToGA clinical trial. ToGA (Trastuzumab for Gastric Cancer) is an open-label, international, phase III clinical trial undertaken across 122 centers in 24 countries[80]. In this trial, 584 patients with HER2-positive advanced gastric and gastroesophageal junction cancer received either chemotherapy (capecitabine or fluorouracil plus cisplatin) plus trastuzumab or chemotherapy alone. Patient median overall survival increases by 2.7 months with chemotherapy and trastuzumab compared to chemotherapy alone (13.8 vs 11.1 months). Notably, an exploratory post-hoc analysis reveals that patients with higher HER2 expression demonstrated greater overall survival[81]. In this study, trastuzumab treatment also significantly increased progression-free survival, time to progression, and proportion of patients achieving an objective response[80].

Since the ToGA trial, additional trials examined the role for trastuzumab in advanced clinical settings. In 2017, Thuss-Patience et. al. led a phase II/III global study (GATSBY), to assess the efficacy and safety of trastuzumab emtansine (a drug antibody conjugate) versus taxane treatment in patients with previously treated HER2- positive advanced gastric or gastro-esophageal cancers[82]. Unfortunately, the results are not consistent with those of the ToGA trial, with no improvement in survival in patients treated with trastuzumab. Further, the role of trastuzumab in the neoadjuvant setting in addition to chemoradiation also shows no survival benefit in patients with HER2-expressing tumors[83]. Other phase III trials investigating trastuzumab in combination therapies edo not demonstrate differences in overall survival[84,85].

Lapatinib is a small-molecule tyrosine kinase inhibitor targeting both epidermal growth factor receptor (EGFR) and HER2. Treatment with lapatinib affords a 9% response rate as a monotherapy against advanced gastroesophageal junction tumors. While this number may seem low, no anti-HER2 agent had previously demonstrated improved survival as a monotherapy prior to this study[86]. Hecht et al. report a phase III trial, termed TRIO-013/LOGiC, that evaluates lapatinib's efficacy in combination with capecitabine and oxaliplatin (CapeOx) for the treatment of EAC. Although the response rate significantly increases compared to placebo (53% vs 39%), patient overall survival does not improve[87].

One novel treatment under investigation is MM-111[71], a bispecific antibody fusion protein binding HER2 and HER3, another receptor tyrosine kinase in the human epidermal growth factor receptor family[88]. Despite promising preclinical results, a phase II clinical trial evaluating MM-111 in combination with trastuzumab and paclitaxel was terminated early due to a lack of efficacy[89]. The JACOB phase III trial investigated the efficacy of pertuzumab, another anti-HER2 agent, with or without trastuzumab and chemotherapy to

treat gastro-esophageal junction cancer. Unfortunately, no significant difference in overall survival exists between the treatment groups[90]. Thus, while HER2 seems to be a promising target based on its overexpression in a subset of EC and the efficacy of its targeting in improving survival in other malignancies, the poor clinical results of anti-HER2 targeted therapies in esophageal cancer signify the necessity for further study of the role of HER2 in the pathobiology of esophageal cancer and the potential role for development of more tumor-specific HER2 targeted treatments.

Vascular endothelial growth factor (VEGF)—Tumors commonly overexpress vascular endothelial growth factor (VEGF) promoting angiogenesis and subsequent tumor growth[91]. Given the increased expression of angiogenic markers associated with aggressive disease subtypes and associated inferior survival in esophageal cancers, targeting angiogenesis is an attractive strategy for this disease[92–94]. In fact, several studies show a correlation between VEGF expression and advanced tumor stage (III/IV) with increased risk for metastasis[95,96]; yet, there is minimal clinical success utilizing it as a target for treatment thus far.

The only FDA approved angiogenesis inhibitor in esophageal cancer is ramucirumab, a monoclonal antibody that binds and blocks the VEGF receptor to prevent the formation of new blood vessels. Both the REGARD[97] and RAINBOW[98] trials demonstrate improved overall survival in patients with advanced EAC after initial chemotherapy treatments with administration of ramucirumab either as a monotherapy or with paclitaxel, respectively. In contrast, results from a phase II clinical trial led by Yoon et. al., show improved overall response of stable disease, but not progression-free survival when ramucirumab is administered with FOLFOX as a front-line therapy to treat metastatic or non-resectable, locally advanced gastric-esophageal junction adenocarcinoma[99].

Apatinib, another VEGF receptor inhibitor, is FDA approved for the treatment of gastric cancer[100,101], and shows promise in clinical trials for the treatment of metastatic esophageal cancer. Results from two clinical trials reveal that apatinib is effective as both second and further-line treatment for advanced esophageal cancer[102,103]. In combination with chemotherapy, apatinib affords similar success and improvement in overall survival[104–106]. Despite the success of apatinib, clinical trials of other VEGF targeting antibodies, such as bevacizumab[107,108], sunitinib[109–112], sorafenib[113–116], pazopanib[117–118], and regorafenib[119–123] all report minimal to no improvement in survival. Hence, VEGF may represent a useful marker for aggressiveness of esophageal cancer subtypes but opportunities remain for improvement of targeting and extension of survival.

Epidermal growth factor receptor (EGFR)—Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein overexpressed in several gastrointestinal malignancies. Ligand binding to the extracellular domain activates EGFR, and subsequent phosphorylation of the intracellular tyrosine kinase initiates several downstream pro-growth pathways including Ras/Raf/mitogen-activated protein kinases and the Akt/mTOR pathway. Approximately 30%−50% of gastro-esophageal malignancies and 19% of squamous cell cancers overexpress EGFR. Further, more aggressive histology and advanced tumor stages correlate with increased levels of EGFR expression[124–126].

Given that EGFR upregulation is common in many cancer types, there are several FDA-approved monoclonal antibody therapies in clinical use across multiple malignancies. These include: cetuximab for the treatment of both metastatic colorectal and squamous cell cancers[127], panitumumab for metastatic colorectal cancer[128], nimotuzumab for gliomas and head/neck cancer[129], and necitumumab for the treatment of non-small cell lung cancer[130]. However, there are no currently approved therapies for treatment of esophageal cancer[131]. The success in other cancer subtypes prompts ongoing investigations towards translating similar therapeutics to esophageal cancer.

Cetuximab is minimally successful as a monotherapy in esophageal cancer. A phase II trial reports that only 3% of patients (one person) demonstrated a partial response to cetuximab monotherapy after previous chemotherapy regimens failed[132]. Cetuximab when used in combination with chemotherapy in the adjuvant setting shows slightly more promise. Two independent phase II trials in patients with advanced gastro-esophageal cancer reveal enhanced response rate with the addition of cetuximab in conjunction with cisplatin/docetaxel[133] or docetaxel alone[134]. However, there is no overall survival benefit. Other EGFR-targeting monoclonal antibodies, such as nimotuzumab[135–138], and panitumumab[139–141] are currently being clinically evaluated; however, as of today, none of these agents demonstrates clinical success in terms of overall survival or disease progression.

In addition to monoclonal antibodies, tyrosine kinase inhibitors (TKIs) are pharmacological agents that inhibit the phosphorylation of specific proteins downstream of EGFR-induced signal transduction cascades. Gefitinib and erlotinib are both FDA approved for the treatment of non-small cell lung cancer[142], and metastatic non-small cell lung cancer/advanced pancreatic cancer[143], respectively. Yet, clinical trials with gefitinib for treatment of esophageal cancer were unsuccessful or terminated early[144,145]. Patient response to erlotinib is greater compared to gefitinib. The outcomes from the SWOG 0127 trial, which examined patients with EAC at the gastrio-esophageal junction, show some efficacy of erlotinib as a first-line therapy[146]. In conjunction with radiotherapy for the treatment of older patients with EC stages I-IV, erlotinib treatment yields a 12% complete response rate, defined as absence of viable tumor in endoscopic evaluation[147]. In a trimodality neoadjuvant setting, erlotinib plus chemoradiotherapy against localized esophageal cancer raises the complete response rate to 29%[148]. These results merit further investigation of TKIs and specifically their impact on the EGFR pathway for esophageal cancer treatment.

Mammalian target of rapamycin (mTOR)—The mTOR pathway plays a pivotal role in cell growth and proliferation, and its dysregulation is linked to tumorigenesis[149,150]. As mTOR upregulation exists in many cancer types, it is a common target for inhibition, with currently three FDA-approved treatments: sirolimus (rapamycin), temsirolimus, and everolimus. In the early 2010s, everolimus was approved for the treatment of renal cell carcinoma, astrocytoma, and HER2-negative breast cancer. With regards to gastric cancer, 56% of gastric cancer patients treated with everolimus as monotherapy achieve disease control as reported by the GRANITE-1 trial, a multicenter phase II and III study[151]. Unfortunately, patient overall survival does not significantly improve, and this finding was confirmed in a subsequent clinical trial[152]. Interestingly, esophageal cancer patients treated with everolimus, both in combination with chemotherapy[153] or as a monotherapy[154], show a

marginal increase in disease control and progression-free survival. These initial studies merit additional follow-up to identify if targeting the mTOR pathway is a viable mechanism to treat esophageal cancer.

A newer target associated with the mTOR pathway is TRIM44, a member of the tripartite motif (TRIM) protein family. TRIM44 promotes tumor growth in non-small cell lung cancer via the mTOR pathway and is of prognostic value for EAC[155]. Moreover, TRIM44 downregulation suppresses ESCC cell proliferation, migration, and invasion, while overexpression promotes these cellular activities[156], making this a promising target for future studies.

Cyclin-Dependent Kinases (CDKs)—Greater than 90% of ESCCs contain alterations to the cell cycle pathway[69]. The two most common cell cycle targets currently under investigation in esophageal cancer are CDK4 and CDK6, which phosphorylate cyclin D to promote cell cycle progression (Figure 4[157]). Cyclin-dependent kinase inhibitors (CDKIs) were first explored in the 1990s, when loss of the endogenous CDKI $p27^{Kip1}$ directly correlated with the progression of esophageal squamous cell carcinoma[158]. Since then, there are numerous FDA-approved CDKI therapies such as palbociclib[159], abemaciclib[160], and ribociclib[161]. Notwithstanding, these inhibitors are currently only in clinical use for breast cancer and are not yet approved for esophageal cancer. Palbociclib is cytotoxic against ESCC *in vitro* with resistant cells demonstrating glutamine dependence[162]. Abemaciclib shows preclinical success against esophageal cancer cells both *in vitro* and *in vivo*[163,164], and clinical trials investigating ribociclib[165] and palbociclib[166] are ongoing. Additional CDKIs are being evaluated *in vitro*, with positive preliminarily results[167–169]. As a result, there are several multi-center clinical trials evaluating these CDKIs[170,171], and other cell cycle targets for the treatment of esophageal cancer.

Yes-associated protein 1 (YAP1)—Yes-associated protein (YAP1), the Hippo pathway transcriptional coactivator, is a recently discovered oncogene and another potential target for new therapies for esophageal cancer[172]. In a Japanese cohort - one of the countries with the highest prevalence of this disease – ESCC over expresses YAP1[173]. Knock down of this gene *in vitro* inhibits proliferation and increases apoptosis in esophageal cancer cells, highlighting the importance of this gene to tumor progression[174,175]. YAP1 plays a key role in several tumor associated pathways, specifically upregulation of both SOX9[176] and EGFR[177], corresponding to increased tumorgenicity and chemoresistance, respectively. The crosstalk between YAP1 and CDK6, as reported by Li et. al., highlights the potential of dual targeting, given that dual inhibition results in enhanced antitumor effect *in vitro* and *in vivo*[178]. Recent success in preclinical trials brings promise for the development of such novel therapies in the future[179].

Claudin 18.2—A recently identified new target in gastric and gastroesophageal junction tumors is isoform 2 of claudin-18 (CLDN18.2). Claudins are components of tight junctions on tumor epithelial cells, and CLDN18.2 is highly expressed in gastric cancer[180]. This discovery led to the design of the monoclonal antibody zolbetuximab to specifically target CLDN18.2. Addition of zolbetuximab to chemotherapy improves overall and progression-free survival in metastatic or unresectable gastric and esophagogastric cancers[181]. Based

on these results, zolbetuximab is currently undergoing expedited FDA review for use in advanced gastric cancers lacking HER-2 expression; while there were no deficiencies cited in the clinical data, FDA approval was set back due to manufacturing concerns. Efficacy of zolbetuximab in the neoadjuvant or adjuvant settings in locally advanced resectable esophageal cancers remains to be determined.

Novel Delivery Mechanisms

Most chemotherapeutics are hydrophobic, resulting in poor solubility, necessitating the use of solvents such as pegylated castor oil for intravenous administration[182]. Additionally, intravenous administration is fraught with pharmacokinetic challenges to deliver sufficient chemotherapeutic to the tumor. In contrast, biological therapies are hydrophilic proteins soluble only in aqueous solution, which possess their own set of challenges for drug delivery including processability, protein denaturation, and retention of activity. Given this cancer's location, oral delivery is a potential alternative delivery mechanism for esophageal cancer, with rapid adsorption into the highly vascularized oral and esophageal mucosa[183], however this route can be limited in a large percentage of esophageal cancer patients with associated dysphagia[184]. Esophageal cancer patients would therefore benefit from development of a delivery system that will increase tumor targeting, bioavailability, and intratumor concentration, while decreasing toxicities and off-target effects. In this section, we discuss four promising delivery mechanisms for treatment of esophageal cancer – nanoparticles, stents, antibody drug conjugates, and chimeric antigenic receptor T cells – and examine their successes and limitations in several recent studies.

Nanoparticles

One solution to improve systemic delivery is to package the drug payload into nanoparticles, which increases the *in vivo* half-life and accumulation at the disease site. These 10–500 nm diameter particles typically encapsulate chemotherapeutics or small-molecule hydrophobic agents and are amenable to surface modification to introduce moieties for tumor targeting. Drug-loaded nanoparticles were first investigated to treat esophageal cancer in the mid-2000s[185–187], culminating in a phase I trial of now FDA-approved abraxane (nab-paclitaxel)[179].

There is extensive preclinical work on carbon-based nanotechnologies as well, such as carbon nanoparticles[188–191], carbon nanotubes[192–195], and graphene[196–198], due to their potential biocompatibility, ease of synthesis, and unique ability to introduce surface modifications. However, these carbon materials, as with most polymer or ceramic nanoparticles, are limited in their ability to efficiently load chemotherapeutics, owing to their physical structure and their hydrophilicity. Zhang et. al circumvent this issue by developing ~100nm hollow carbon spheres which contain 132% more drug than conventional carbon spheres. When administered *in vivo*, these doxorubicin-loaded hollow carbon spheres show improved antitumor activity, increased drug accumulation at the tumor site, and reduced off-target toxicities in vital organs, such as the heart and kidney[199].

Fluorescent self-assembling cyclic peptide nanoparticles, as reported by Fan et. al., are biocompatible, biodegradable, capable of loading chemotherapeutics, and amenable to

functionalization with active targeting moieties. Specifically, loading of epirubicin (EPI), a chemotherapeutic used to treat some esophageal cancer patients, and conjugating a tumor-honing peptide (RGD), affords a NP which selectively targets both EAC and ESCC cells, while also affording anti-tumor activity with significantly less side effects compared to EPI alone in a murine model (Figure 5[200]).

Micelles are an aggregation of amphiphilic polymers that form a colloidal suspension and are ideal for encapsulating hydrophobic drugs in their core. Traditional micelles comprise a surfactant with a hydrophilic head and a hydrophobic carbon chain, and readily encapsulate chemotherapeutics such as paclitaxel, doxorubicin, and cabazitaxel[201–203]. As reported by, Fu et. al., poly(caprolactone)-pluronic micelles loaded with doxorubicin are readily taken up in multiple esophageal cancer cell lines and when administered *in vivo* decrease tumor volumes compared to saline controls[204]. These polymeric micelles are easily functionalized, affording synthesis of active targeting systems. Conjugation of a targeting peptide to the exterior of the micelles results in specific targeting of esophageal cancer cells, increasing the overall efficacy of the treatment. Specifically, conjugation of the SNFYMPL peptide onto their paclitaxel loaded PEG-DSPE micelles target the epithelial cell adhesion molecule (EpCAM, upregulated in EAC), resulting in greater cellular uptake *in vitro*, superior tumor reduction, and extended survival *in vivo* compared to traditional, non-targeted micelles[205].

Functional nanoparticles which respond to stimuli, be it a change in pH, redox state, or ionic strength[206–211], are also of significant interest. An elegant example of responsive nanoparticles to treat esophageal cancer is reported by Matsumoto et al., who describe a disulfide bond crosslinked core poly(ethylene glycol)-*block*-poly(l-lysine) NP loaded with an siRNA therapeutic. The siRNA releases upon cleavage of the disulfide linkages within the tumor[212]. A similar disulfide cross-linked micelle, composed of PEG_{5k}-Cys_4-L_8-CA_8 telodendrimers, efficiently encapsulates docetaxel or AZD8186, a PI3K inhibitor, as they are both hydrophobic. Intravenous delivery of these nanoparticles reduces tumor burden in an *in vivo* model of esophageal cancer. When loaded together, the treatment halts growth of the primary tumor, demonstrating the advantage of responsive, dual-loaded systems to treat esophageal cancer[213].

Biocompatible, nonimmunogenic nanoparticles composed of amphiphilic phospholipids are easily manufactured and are widely available from natural sources. These “cell-like” carriers are capable of loading both hydrophobic and hydrophilic drugs and can be further modified to contain active targeting moieties on the exterior[214–216]. Ren et. al. describe a red blood cell membrane functionalized carrier system with the internalizing RGD peptide and an EGFR antibody to create an ESCC tumor targeting nanocarrier with tumor penetration capabilities for paclitaxel delivery[217]. Ren et. al.’s work examplifies how combining nanoparticles and the tumor targets discussed above represents the future for esophageal cancer treatments. Li et. al. utilize gold nanoparticles with aptamers to target both EGFR and HER2, and demonstrate unique targeting capabilities in vitro[218]. Liu et. al. target VEGF with calcium phosphate nanoparticles, and report *in vivo* efficacy[219]. Additional examples include Xia et. al. use of targeting mTOR with artesunate-loaded solid lipid nanoparticles[220].

Stents

The two key challenges to systemic chemotherapy delivery are limited drug accumulation in tumors and off-target toxicities. This is especially true for tumors which are dispersed throughout an area, are present in minimally vascularized tissue, or are exposed to significant exogenous fluid flow, such as the esophagus. Local delivery is a potential solution, such as the delivery of a chemotherapeutic via a stent placed endoluminally at the disease site. Stents are primarily used as a palliative measure to treat malignant dysphagia caused by esophageal cancer, particularly in the metastatic or unresectable setting[221]. The advantages of using a stent in combination with chemotherapy for treatment of esophageal cancer include palliation of esophageal tumor obstruction, enhanced patient quality of life through improved oral intake, and drug delivery directly to the tumor site at the esophageal mucosal surface. Drug-coated stents originated in the mid-1990s when heparin-coated metal stents were implanted to prevent thrombosis in patients with stable angina pectoris[222,223].

Won et. al. describe an implanted self-expanding metal stent embedded with a radioisotope to provide intraluminal palliative brachytherapy in canines[224]. This first trial of a chemo-loaded stent therapy for esophageal cancer entailed use of a metallic stent coated with 5-fluorouracil. In this model, burst release occurs over the first 10 days[225]. While this stent design leaves significant room for improvement, this study demonstrates the principle of local drug delivery through an esophageal stent.

Optimization of a novel drug eluting stent specifically designed for the esophagus requires intricate examination of each component (Figure 6[226]). Specifically, biocompatibility and pharmacokinetics are the primary parameters of interest, as they are closely tied to efficacy. Initial evaluation is typically performed *in vitro*, however work by Shaikih et. al., reveal that this model is not an accurate depiction, as drug uptake heavily depends on the permeability of the esophageal tissue[227]. To prolong drug delivery and enhance efficacy, one employs surface modified metallic stents. Jeon et. al., describe a thin nano-networked silica film on top of a sirolimus-loaded stent that affords a twofold delay in release compared to the control[228]. Many groups leverage these exterior coatings to increase biocompatibility and limit complications such as blockage, inflammation, perforation, and leakage[229–231]. For example, Xue et al. report a film comprised of hyaluronic acid and poly-dopamine, which yields a biocompatible and hemocompatible material compared to the standard poly(dimethylsiloxane) coating[232]. Wang et. al., describe the release kinetics from a stent using the intrinsic properties of their polymeric coating: crack propagation. The release kinetics of both cisplatin and 7-ethyl-10-hydroxycamptothecin are strain-dependent[233]. Zhang et. al. demonstrates that chemotherapeutic release is not necessary. By immobilizing a cytotoxic polymer (poly-ethylenimine) on top of a biocompatible polydopamine film coating, they demonstrate anti-tumor properties with tunable toxicity based on polymeric molecular weight[234].

One approach to further control drug release *in vivo*, is to use near-infrared (NIR) irradiation which can penetrate tissue and alter the stent structure via the surface plasmon resonance effect. In doing so, the rate of drug release increases and it serves as a source for photothermal therapy. Lee et. al. demonstrate this principal using gold-coated nanoturf structures. Here, the stent slowly releases doxorubicin until irradiated with NIR light,

causing a spike in drug release. In a murine model, the stent in combination with the photothermal effect shows increased effiacy[235]. However, clinical translation may be limited due to the short depth of NIR penetration and, therefore, other modalities such as low-level magnetic fields (0.01–0.1 T) are being investigated. Jin et al. report a magnetic field-responsive paclitaxel-loaded stent comprised of nitinol and 1-hexadecanol in which paclitaxel release is due to the magnetocaloric effect[236].

Despite these advances in drug-loaded stent technology, the hydrophobic drug that is eluted from a drug-coated stent still suffers from poor bioavailability and tumor uptake[237]. The partnership of a nanoparticle-coated stent leverages the slow, controlled release of nanoparticles with the local, structural support of the stent. Xiao et. al. establish this technique by electrospinning an albumin-conjugate onto an esophageal stent for delivery of a photosensitizing agent for photodynamic treatments. This methodology is likely transferrable to a chemotherapeutic[238]. The combination of nanoparticle-stents and phototherapy shows success in preclinical development; Cho et al. and Park et al. both utilize gold-nanoparticle coated stents, which, with NIR irradiation, locally heat to prevent granulation tissue formation and hyperplasia, respectively[239,240]. This work could be translated to the treatment of esophageal cancer, using phototherapy for tumor ablation. The fusion of stents and nanoparticles is an attractive approach to increase local drug delivery in esophageal cancers. Nevertheless, there are only a few recorded cases of esophageal cancer patients implanted with a drug-coated stent, with currently no ongoing clinical trials[241]..

Drug Conjugates

Another alternative delivery platform is an antibody-drug conjugate (ADC). ADCs rely on the antibody as a homing mechanism to carry a highly chemotherapeutic agent to a specific target (Figure 7[242]). With just over ten FDA-approved treatments, ADCs are at the forefront of modern medicine[243,244]. Significant pre-clinical studies are underway to identify target tumor surface antigens via high-throughput screening and to assess *in vivo* efficacy of new compositions[245]. Trastuzumab deruxtecan is one FDA approved ADC example which leverages a herceptin antibody and the topoisomerase inhibitor, deruxtecan, for the treatment of HER2-positive breast cancer. When used in combination with chemotherapy for the treatment of patients with advanced HER2-positive gastric or gastroesophageal adenocarcinoma[246], the median disease-free survival significantly extends in patients with the dual treatment, compared to chemotherapy alone. Following successes in phase I[247] and phase II[248–250] trials against gastric cancer, median disease-free survival slightly improves in patients with HER2+ EAC when combined with trimodality treatment in a phase III trial (NRG Oncology/RTOG-1010). However, the results are not statistically significant, and further investigations are warranted[251].

The ADC composed of a bispecific antibody directed against the tumor associated antigens (TAAs) mucin-1 (MUC1) and human epidermal growth factor receptor (EGFR), linked to antimitotic agent (hemiasterlin; M1231) is under evaluation as a monotherapy for the treatment of esophageal cancer[242]. Knuehl et. al. report, in a poster at the 2022 AACR meeting, impressive therapeutic responses in two different patient-derived xenograft models[252], and M1321 is currently undergoing a phase I clinical trial as a single agent

for the treatment of esophageal cancer[253]. Results from two other recent phase I trials with tisotumab vedotin[254] and sacituzumab govitecan[255] show serious adverse side effects during dosing, which has dampened enthusiasm for these particular agents. However, GPC1-ADC(MMAE)[256], enfortumab vedotin[257], and Fv-LDP-D3-AE[258] all show *in vitro* and *in vivo* efficacy and merit their own clinical investigations, showing promise for use of ADCs against esophageal cancer.

ADCs are not the only drug conjugates currently under investigation; peptides are also capable carriers that efficiently target tumors. Peptide-drug conjugates (PDCs) are small, with high drug-loading, and exhibit excellent cell permeability. Lam et. al. report a synthetic peptide library to identify specific ligand-binding capabilities[259], which can be leveraged to target esophageal cancer cells. Wang et. al. describe that DM1, a promising chemotherapeutic that is also highly toxic, when combined with a peptide, LLC2B, inhibits tumor growth both *in vitro* and *in vivo*[260]. While these PDCs are actively under investigation[261–263], there has been minimal work leveraging this technology for esophageal cancer. There is clearly a need for future research in this space, with potential to engage other chemotherapeutics previously thought non-viable due to severe off-target toxicities.

Chimeric Antigenic Receptor T cells.

Synthetic biology is another emerging field profoundly impacting cancer treatment, with chimeric antigenic receptor T cells (CAR-T) or T cell receptor T cells (TCR-T) being a prime example. Clinically, T cells are harvested from the patient, engineered to target a specific antigen on the cancer cell surface, and then introduced into the patient's immune system. Recent clinical successes in melanoma[264], sarcoma[265], and colorectal carcinoma[266] are prompting clinical investigation for the treatment of esophageal cancer[267,268]. Given the significant research in melanoma, lung, breast, ovarian, and bladder cancers, antigens are known which are upregulated in epithelial carcinomas but with limited expression in healthy normal adult tissue[269–274]. Far fewer upregulated antigens are known for esophageal cancer, with candidates including MUC1, HER2, EpCAM, CLDN18.2, MAGE-A3, MAGE-A4, and NY-ESO-1[275,276,277]. Success targeting these antigens with CAR-T and TCR-T therapies both *in vitro, in vivo*, and in clinical trials provides motivation for further studies[265,278–280]. Lu et al. report a partial response with treatment using autologous MAGE A3 engineered T cells[281] with only minimal adverse reactions. In contrast, Morgan et al. note that some patients suffered from neurological toxicities[282]. Kageyama et al., describe the first clinical study using CAR T cells possessing the MAGE-A4 antigen in combination with sequential MAGE-A4 peptide vaccinations in nine patients with recurrent esophageal cancer[283]. Transduced T cells are present in the peripheral blood at one month for all patients, and in five patients they persisted for more than five months. The persisting cells maintain *ex vivo* antigen-specific tumor reactivity. Of the nine patients, three patients who had minimal tumor lesions at baseline survived for more than 27 months, while the remaining patients demonstrated tumor progression within 2 months following treatment. No adverse events or toxicity were noted[283]. Several on-going trials with anti-MAGE-A4 expressing T-cells, as well as other targeted TCRs will offer further insight into efficacy of this approach[284–287]. Several other targets for CAR-T and TCR-T cell therapies, as well as CAR-Natural Killer (CAR-NK) cells, are currently being explored.

Conclusion

Esophageal cancer is one of the deadliest malignancies, yet treatment options remain limited due to insufficient research in this field. Trimodality therapy with neoadjuvant chemoradiation and esophagogastrectomy are improving survival outcomes, however only patients with local or locally advanced disease are candidates for surgical resection. By expanding knowledge of esophageal cancer-specific disease targets and delivery platforms, the potential for development of more effective treatment options is promising. Several of the discussed approaches merit further clinical evaluation and refinement to address the unique issues associated with esophageal cancer. Recent advances in immunotherapy, new therapeutic targets, and new potential approaches, such as local drug delivery via device platforms or ADCs, hold substantial promise to advance the field. With recent early and promising clinical trial results in many of these areas, the next decade will likely hold significant advances in patient survival as well as quality of life.

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SEER Stage	AJCC Stage	Treatment	Five-year survival rate
Localized	I (T1, N0, M0) to IIB (T3, N0, M0)	Endoscopic mucosal resection Esophagectomy if invasion beyond the submucosa without lymph node involvement	41%
Regional	IIB (T1-2, N1, M0) to IIIC (all T classifications, N3, M0)	Esophagectomy with lymphadenectomy Neoadjuvant/adjuvant chemotherapy or chemoradiation therapy	23%
Distant	IV	Brachytherapy Esophageal bypass surgery Jejunostomy or gastrostomy tubes Palliative chemotherapy Self-expanding mucosal stents Antibody (Trastuzumab) therapy	5%

Figure 1.

Table of treatments and associated 5-year survival rate for esophageal cancer, organized by staging classification. Adapted from ref 14.[14]

SEER = Surveillance, Epidemiology, and End Results. AJCC = American joint Committee on Cancer.

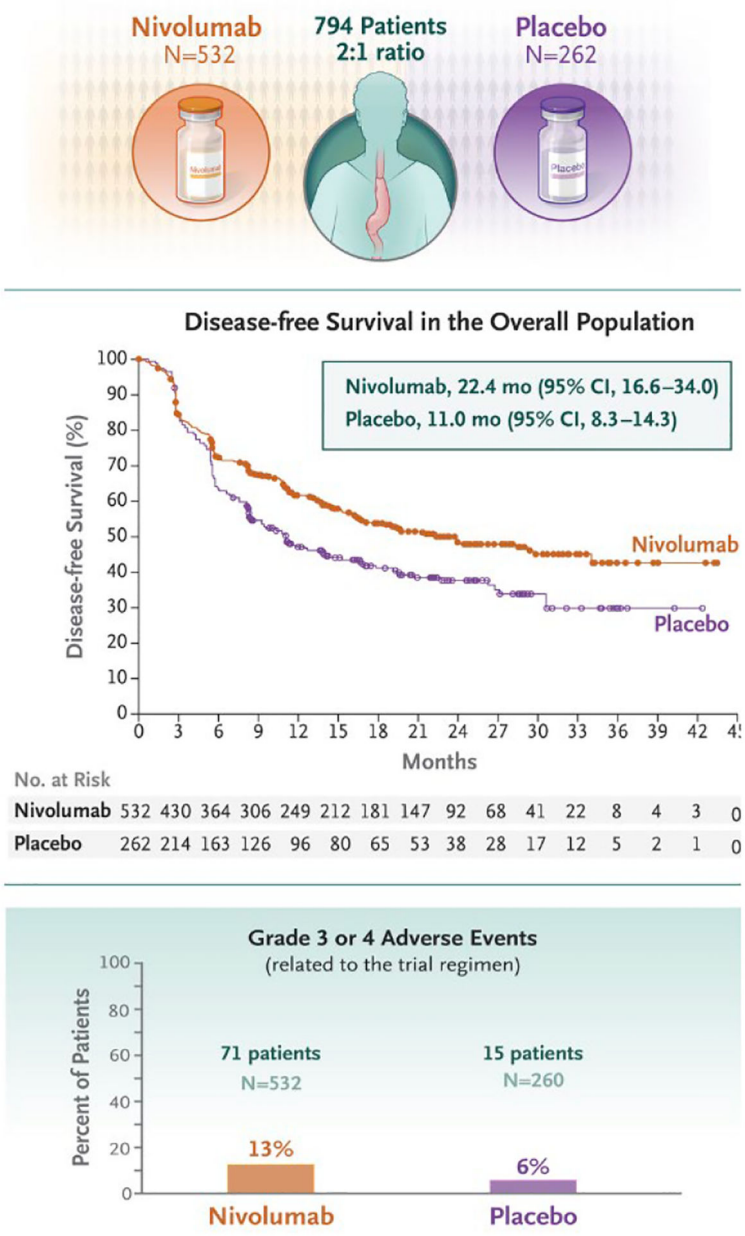

Figure 2.

Illustration summary of pivotal Checkmate 577 trial, indicating efficacy of nivolumab[56.] Reproduced with permission from ref. 56. Copyright 2021 New England Journal of Medicine.

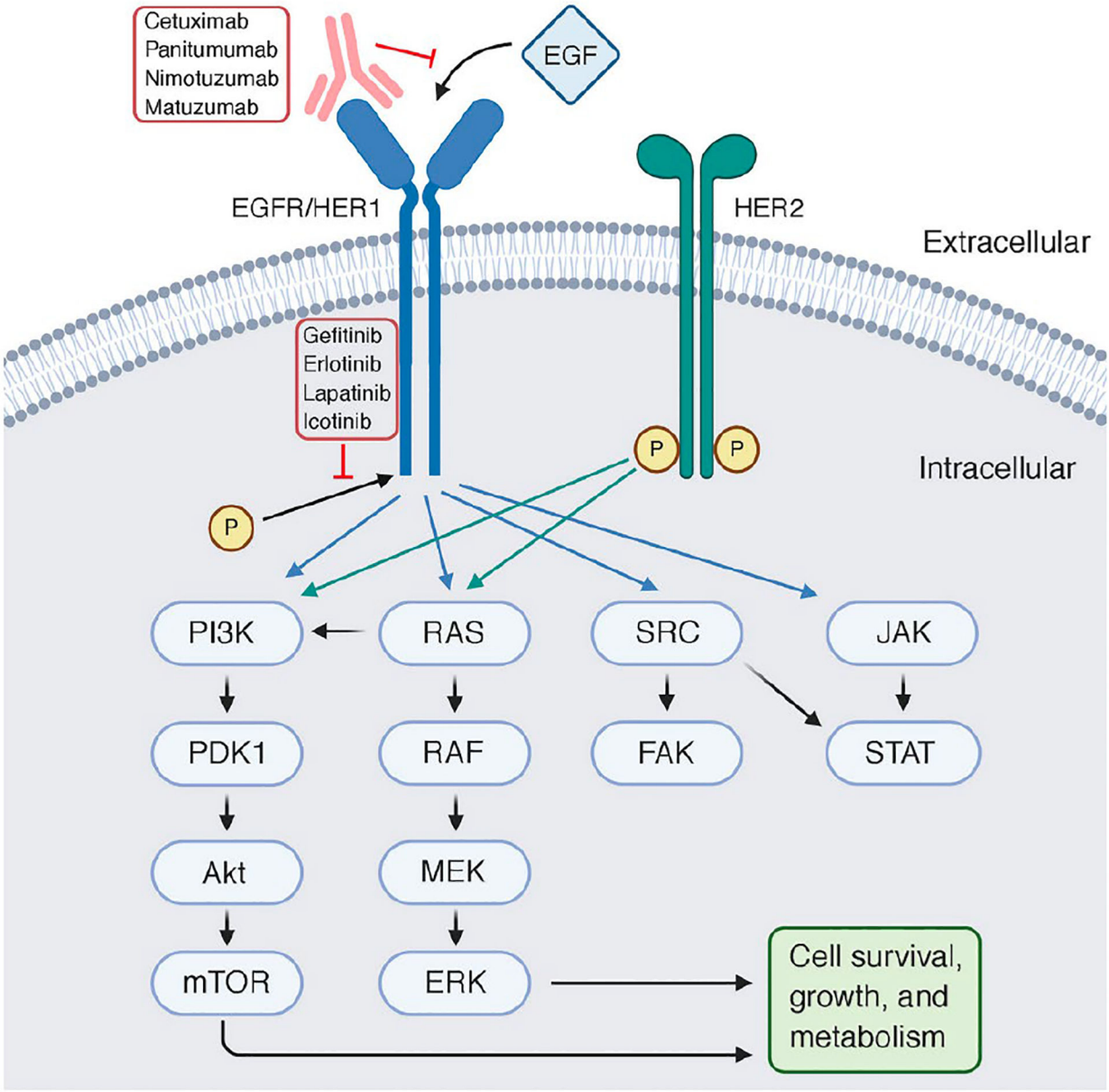

Figure 3.

Illustration of the EGFR signaling domains and its downstream pathway, with examples of inhibition from monoclonal antibodies extracellularly and small molecule inhibitors intracellularly[70]. Reproduced with permission from ref. 70 (CC BY).

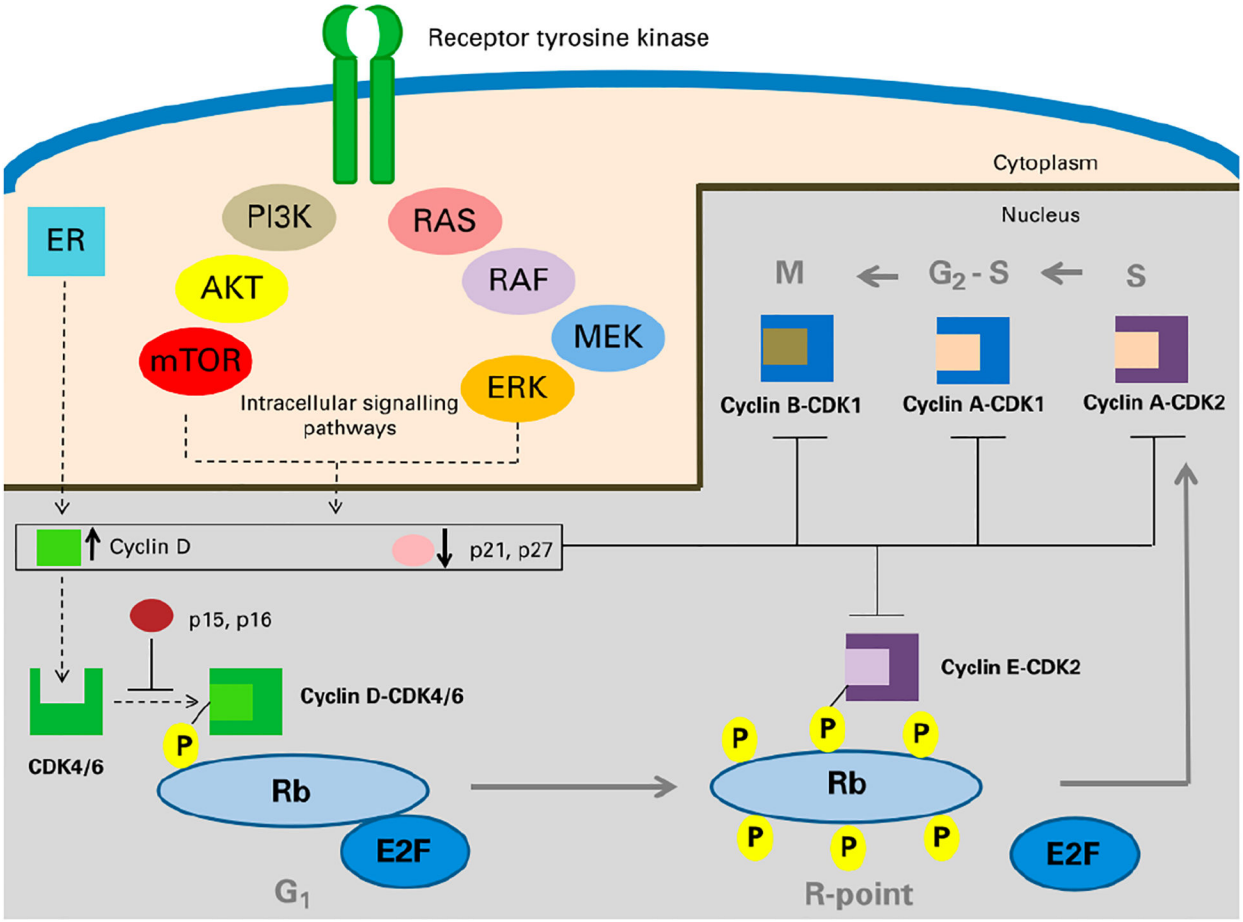

Figure 4.

Illustration of the role of CDK4/6 in the cell cycle progression[157] Reproduced with permission from ref. 157. Copyright 2017 Wolters Kluwer.

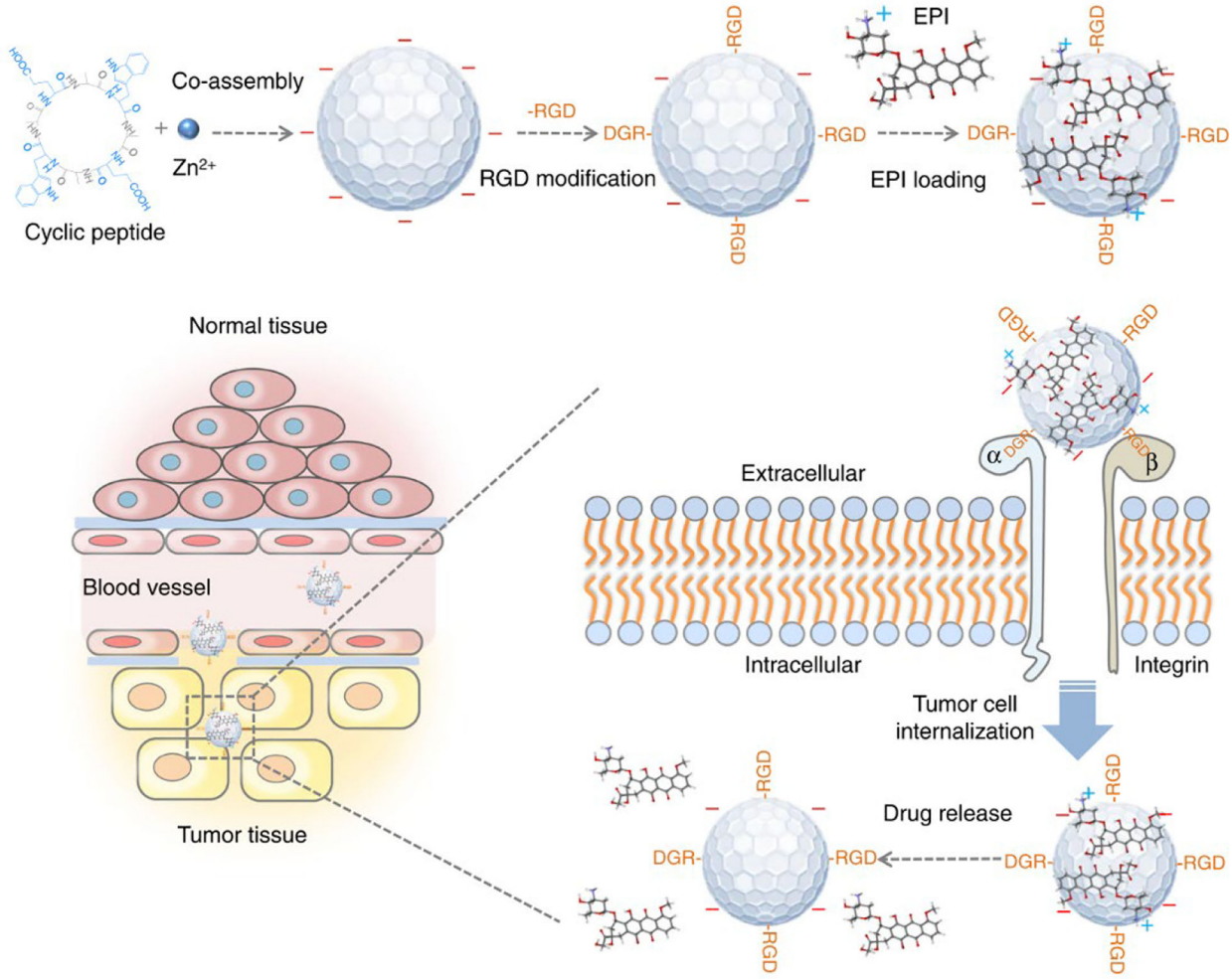

Figure 5.

Diagram of EPI-loaded self-assembling peptide nanoparticles and their tumor-honing ability due to the RGD ligand[200] Reproduced with permission from ref. 200 (CC BY).

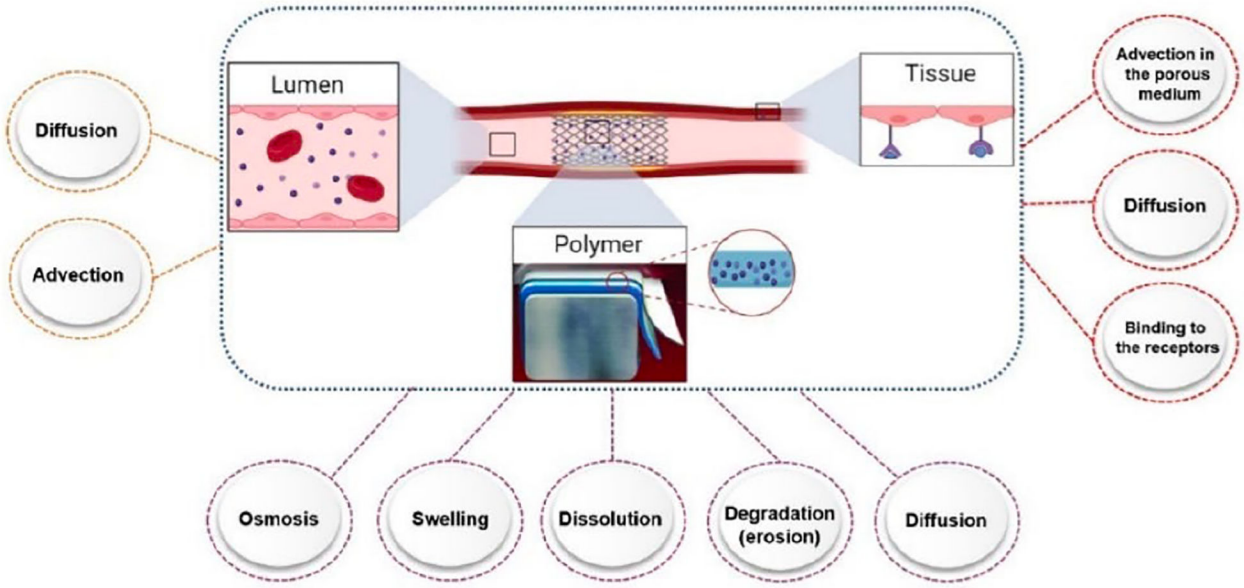

Figure 6.

Diagram of a drug eluting stent and the components that impact release kinetics and efficacy[226] Reproduced with permission from ref. 226 (CC BY).

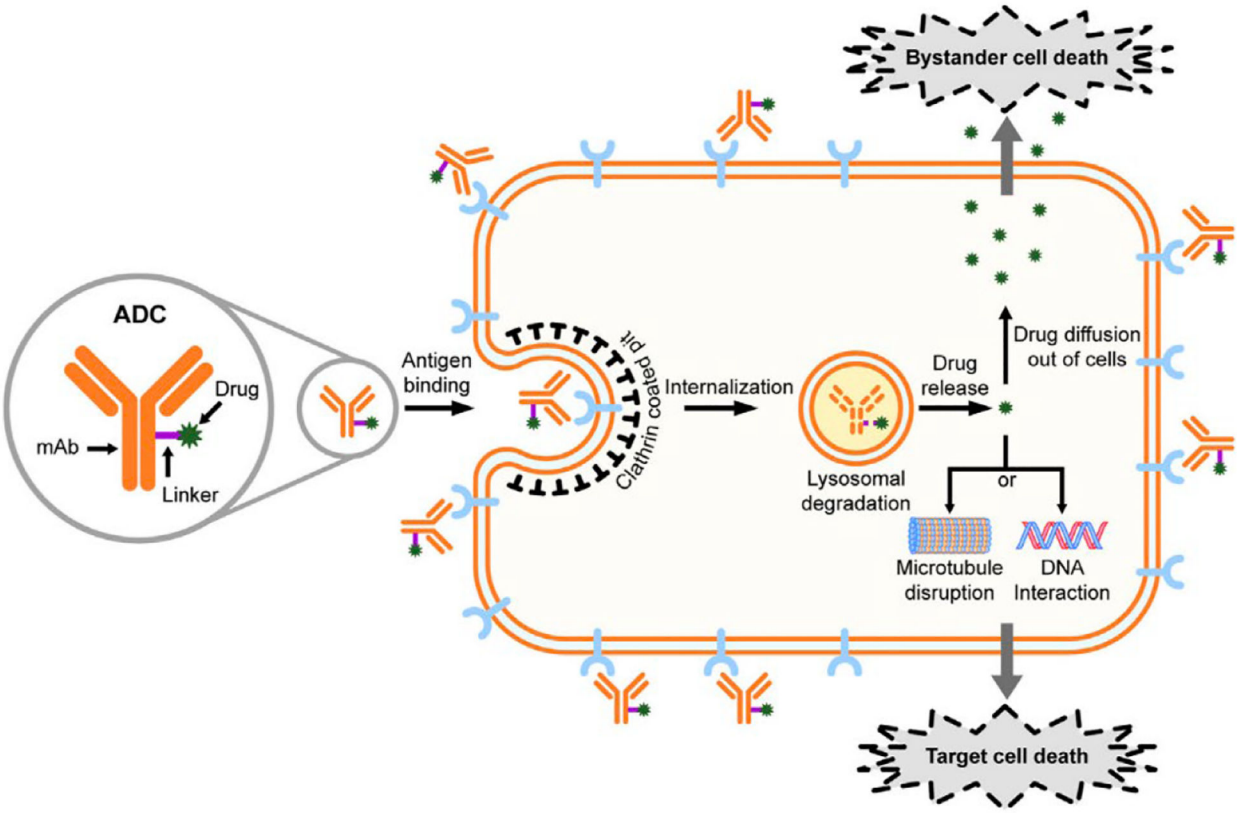

Figure 7.

Depiction of an ADC and the mechanism of cellular delivery/apoptosis[242] Reproduced with permission from ref. 242. Copyright 1997 Elsevier.