



Published in final edited form as:

CA Cancer J Clin. 2018 November ; 68(6): 488–505. doi:10.3322/caac.21498.

Local Cancer Recurrence: The Realities, Challenges, and Opportunities for New Therapies

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Abstract

Locoregional recurrence negatively impacts both long-term survival and quality of life for a number of malignancies. For appropriate-risk patients with an isolated, resectable local recurrence, surgery represents the only potentially curative therapy. However, oncologic outcomes remain inferior for patients with locally recurrent disease even after macroscopically complete resection. Unfortunately, these operations are often extensive with significant perioperative morbidity and mortality. This review highlights selected malignancies (mesothelioma, sarcoma, lung cancer, breast cancer, rectal cancer, peritoneal surface malignancies) in which surgical resection is a key treatment modality and where local recurrence plays a significant role in overall oncologic outcome with regards to survival and quality of life. For each type of cancer, the current, state-of-the-art treatment strategies and their outcomes are assessed. The need for additional therapeutic options is presented given the limitations of the current standard therapies. New and emerging treatment modalities, including polymer films and nanoparticles, are highlighted as potential future solutions for both prevention and treatment of locally recurrent cancers. Finally, we identify additional clinical and research opportunities, and propose future research strategies based on the varying patterns of local recurrence among the different cancers.

Keywords

local recurrence; mesothelioma; sarcoma; lung cancer; breast cancer; rectal cancer; peritoneal surface malignancies; drug delivery; polymers; nanoparticles

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Conflict of Interest Disclosures: DAM – none; RL – none; MWG- has ownership interest in AcuityBio and Ionic Pharmaceuticals; YLC – none; CPR – none

Introduction

In 2018, there will be a projected 1.7 million new cancer cases and approximately 600,000 cancer deaths in the United States.¹ Advances in surgery, chemotherapy, radiotherapy, and newer modalities such as molecularly targeted therapies and immunotherapy, have significantly reduced morbidity and improved survival over the past decades. Despite this progress, cancer remains the second leading cause of death in the United States, after cardiovascular disease.² Most of the recent attention in antineoplastic therapy focuses on systemic treatments for metastatic disease, a point at which long-term cure is rarely possible. To reliably cure cancer, local control is essential. However, locoregional recurrence (LRR) is a clinically relevant, predominant pattern of failure in many malignancies. This review describes current therapeutic strategies to both prevent and treat local cancer recurrence in six selected malignancies: rectal cancer, breast cancer, mesothelioma, non-small cell lung cancer, retroperitoneal sarcoma, and peritoneal surface malignancies (Figure 1, Table 1). Local recurrence after surgical resection plays a major role in decreased survival and quality of life for patients with these cancers. Furthermore, these malignancies represent a range of important oncologic principles to consider when assessing present and future therapies to treat and prevent local recurrences. Patterns and risk factors for locoregional recurrence are highlighted. Finally, opportunities for clinical improvement are identified, and novel therapeutic strategies in preclinical development are discussed, specifically in the context of these six malignancies, but potentially applicable broadly.

Rectal Cancer

Approximately 43,000 cases of rectal cancer are diagnosed in the United States annually.¹ Advances in surgical techniques and neoadjuvant/adjuvant therapies have significantly decreased LRR rates. Half of rectal cancer recurrences are locoregional (anastomotic, extravisceal pelvic, nodal) without distant metastatic disease.³ Large surgical series from the 1980's reported LRR rates ranging from 10–32%,⁴ with approximately one-third of patients being candidates for re-resection. While patients undergoing re-operation achieved a 5-year overall survival (OS) of 18–49%, 3–8% died perioperatively. Non-surgical candidates fared worse with 5-year OS under 5%.⁵ Risk factors for local recurrence include anastomotic leak, non-R0 resection, intraoperative tumor perforation, high-grade pathology, and lack of adjuvant therapies.⁶ Local recurrence in rectal cancer is associated with lifestyle-altering symptoms such as rectal bleeding, bowel obstruction, chronic pain, fistulas, malodorous tumor discharge, tenesmus, and pelvic sepsis.⁷

The two main strategies to reduce LRR in rectal cancer are more extensive surgery and neoadjuvant (chemo)radiation (Table 2). In Japan, the standard abdominoperineal resection includes a wide perineal skin incision and resection of the levator ani muscle and ischioanal adipose tissue, with additional dissection of the obturator and iliac lymph nodes when stage II/III disease is suspected. In a randomized trial enrolling 701 patients, the LRR rate after this more extensive surgery was 7.4% (versus 12.6% with mesorectal excision alone, $p=0.024$).⁸ More extensive surgery resulted in less presacral LRR; however, up to 96% of patients developed some degree of sexual dysfunction.⁹ In contrast, total mesorectal excision (TME), the standard surgical approach in Western countries, employs a dissection

between the parietal and visceral endopelvic fascial layers. TME preserves the pelvic autonomic nerves, with lower rates of sexual dysfunction, ranging from 19% to 69%.¹⁰

The use of neoadjuvant (chemo)radiation therapy is generally considered standard for stage II and III rectal cancers following two large randomized controlled trials, the Dutch TME study¹¹ and the MRC CR07 trial.¹² The Dutch trial randomized 1,417 patients to either receive preoperative radiotherapy and TME or TME alone. The 5-year LRR rates were 4.6% in the combined therapy group and 11.0% in the surgery alone group ($p<0.001$), with the largest reduction noted in anastomotic recurrence rates (0.7% versus 2.7%, $p=0.003$).¹¹ The CR07 trial randomized 1,350 patients with resectable rectal cancers to receive either preoperative radiotherapy or selective postoperative chemoradiation with intravenous (IV) 5-fluorouracil. Preoperative radiotherapy significantly lowered 3-year LRR compared to selective adjuvant therapy (4.4% versus 10.6%, $p<0.0001$) and improved disease-free survival (DFS), but did not impact OS, thus demonstrating an important role for additional local therapy in the prevention of locoregional recurrence.¹²

However, neoadjuvant chemoradiation significantly increases morbidity. To reduce this risk, patients undergoing a low anterior resection after preoperative radiotherapy often receive a proximal diverting ileostomy for anastomotic protection.¹³ In a randomized trial of 166 patients, diversion was associated with significantly lower anastomotic leak rates (6.4% vs. 16.7%, $p=0.0443$) and lower re-operation rates for leaks (2.1% vs. 15.2%, $p=0.0217$).¹⁴ However, diverting ileostomies can have their own complications including readmission for dehydration, stoma prolapse, small bowel obstruction,¹⁵ and patients need a second operation to reverse the ostomy. Furthermore, pelvic radiotherapy independently adds significant morbidity, with a meta-analysis on long-term function showing significantly higher rates of stool incontinence (risk ratio 1.67, $p<0.0001$).¹⁶ In the Dutch trial,¹¹ patients receiving preoperative radiotherapy experienced significantly more long-term sexual and bowel dysfunction.^{17,18}

More recently, a phase II clinical trial of 32 patients with stage II to III rectal cancer evaluated selective use of neoadjuvant chemoradiation for patients who do not respond to chemotherapy alone.¹⁹ Thirty of the patients (94%) who received neoadjuvant FOLFOX/bevacizumab (6 cycles) achieved a radiographic response and proceeded to TME without radiotherapy. The 4-year local recurrence rate was 0% and the 4-year DFS was 84%. A multicenter, randomized phase III trial (PROSPECT) is currently recruiting to further explore this potential therapeutic option.

An alternative strategy for patients with locally advanced rectal cancers is the use of intraoperative radiotherapy (IORT). While two randomized trials showed no LRR or OS benefit with addition of IORT,^{20,21} a pooled retrospective analysis of over 600 patients reported that IORT significantly reduced LRR rates in patients with margin-positive resections.²² Complication rates with IORT range from 5% to 60%, including wound complications in up to 40% of patients and gastrointestinal fistulae and ureteral injury in 2–12%.²³

Despite the notable advances in surgical and adjuvant therapy over the past few decades, LRR rates for rectal cancers remain between 4% and 8%, and the more extensive surgery and adjuvant therapies all come with increased patient morbidity. Without treatment, patients with LRR suffer a shortened life expectancy and often a poor quality of life.²⁴ Chemoradiation therapy alone extends OS to 12–15 months, but it is not curative.²⁵ Approximately 40% of patients with LRR are candidates for surgery with curative-intent, though surgery can be challenging.²⁶ Although a macroscopically complete resection with negative margins (R0) is the goal, a macroscopically complete resection with positive margins (R1) or a macroscopically incomplete resection (R2) may be inevitable, with survival consequences. A review of 583 patients with locally recurrent rectal cancer who underwent surgery (approximately 60% R0) reported 5-year OS of 44%, 26%, and 10% for R0, R1, and R2 resections, respectively.²⁷ Furthermore, anastomotic recurrences, for which re-resection is more straightforward, are less common in the era of neoadjuvant therapy. Thus, LRR often requires extensive pelvic exenterations, with lower rates of success.²⁷

One newer area of active investigation for this disease is immunotherapy. Programmed death-ligand 1 (PD-L1) expression is upregulated in rectal adenocarcinomas treated with chemoradiation. Thus, checkpoint inhibitor immunotherapy may impact outcomes and redefine the role for surgery in the future.²⁸

Breast Cancer

Breast cancer is the second leading cause of cancer mortality in females, accounting for 40,920 deaths in 2018.¹ The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted randomized controlled trials in the 1970's and 1980's that drastically changed surgical management. The NSABP B-04 trial randomized 1,665 women to receive a radical mastectomy, a total mastectomy alone (removal of all breast tissue with limited axillary lymphadenectomy), or total mastectomy plus irradiation. The 25-year follow-up results from this trial showed no significant difference in DFS or OS among the three groups.²⁹ Subsequently, NSABP B-06 randomized 1,851 women with stage I/II breast tumors to total mastectomy, partial mastectomy, or partial mastectomy plus breast irradiation. With 20 years of follow-up, there was no difference in OS or DFS.³⁰ However, only 10% of women who underwent mastectomy developed LRR (chest wall), compared to 39% after partial mastectomy alone and 14% partial mastectomy with postoperative radiotherapy ($p < 0.001$).³⁰ Together, these studies have confirmed that less extensive surgery with appropriate use of local therapy, in this case radiotherapy, results in equal survival outcomes as more radical surgery, though the LRR rate may be higher.

The extent of axillary surgery for breast cancer also changed. NSABP B-32 randomized 5,611 women undergoing surgery for invasive breast cancer and clinically negative axillary lymph nodes to axillary lymph node dissection (ALND) or sentinel lymph node (SLN) biopsy, with completion axillary dissection performed in patients found to have a positive SLN.³¹ There was no difference in LRR, OS, or DFS. Based on this study, SLN biopsy replaced routine ALND for women with clinically node-negative breast cancer. More recently, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial randomized 891 women with T1-T2 invasive breast cancers, clinically negative nodes, and

1–2 positive SLNs to either undergo completion axillary dissection or no further surgery. There was no difference in 5-year OS, DFS, or LRR rates, thereby further limiting indications for completion ALND.³²

Local recurrence patterns differ based on initial surgical approach and may involve chest wall, residual breast after breast conservation therapy (BCT), or lymph nodes. Not surprisingly, management of LRR depends on initial therapy. Neoadjuvant chemotherapy is often used to enable BCT (partial mastectomy followed by whole-breast irradiation).³³ The two most significant risk factors for LRR after BCT are lack of local radiotherapy and positive margins.³⁴ Other risk factors include younger patient age, large tumor size, high grade, and absence of hormone receptors.³⁵ A meta-analysis of 17 randomized trials including 10,801 women reported a 10-year LRR of 25% in those not receiving radiotherapy and 8% in those that did receive radiotherapy.³⁶ Recurrences were noted later after BCT than after mastectomy (median 3–4 years versus 2–3 years).³⁷ The increased use of partial breast irradiation,³⁸ induction chemotherapy,³³ and SLN biopsy may impact the future rate and management of LRR.

For women who develop an isolated LRR within the breast after BCT, the current standard of care is further surgery, generally a mastectomy. The 5- and 10-year OS rates after salvage mastectomy of a locally recurrent breast cancer are 84% and 71%, respectively.³⁹ LRR within the breast parenchyma is associated with better survival than extramammary LRR (hazard ratio [HR] 2.58 versus 5.85; 5-year OS 60% versus 24%).³⁵ The 3-year OS is worse for women with a shorter LRR disease-free interval (<2 years; 61.9% vs. 89.3%, 95% CI for HR 0.435–0.668).³⁵ A prospective trial of 39 patients who underwent a repeat partial mastectomy with interstitial brachytherapy reported a 5-year LRR rate of 7% and 5- and 10-year OS of 87% and 77%, respectively.⁴⁰ In a randomized trial of 162 women undergoing surgery for locally recurrent breast cancer, those receiving adjuvant chemotherapy had significantly better 5-year DFS than those who did not (69% vs 57%, $p=0.046$).⁴¹

Regional nodal recurrences after BCT are less common than isolated intramammary LRR (1–6% of patients), thus arguing that approaches to sterilize the local tumor bed and intramammary tissue could be improved.^{35,42} Surgery for regional nodal recurrences in the absence of distant metastatic disease may improve survival.⁴² Among 165 patients with extramammary LRR enrolled in NSABP trials, recurrences were confined to the axillary in 47 patients, supraclavicular nodes in 81, chest wall or scar in 20, or multiple or other sites in 17.³⁵ Those with an isolated axillary nodal LRR had better 5-year DFS than other extramammary LRR (31.5% versus 12.1%; $p>0.05$).

The 10-year LRR risk is lower after mastectomy than BCT (8–12% vs. 15–20%).^{35,43,44} Post-mastectomy LRRs are usually confined to the chest wall and diagnosed on physical exam. The remainder present with local and regional nodal recurrence, most commonly supraclavicular nodes.⁴⁵ Approximately two-thirds of these LRR are isolated without evidence of synchronous distant metastases,⁴⁶ highlighting the potential importance of locoregional treatment strategies. The two major risk factors for post-mastectomy LRR are primary tumor size greater than 4 cm and 4 or more positive axillary lymph nodes.⁴⁵ Other risk factors include younger age, negative hormone receptor status, and lymphovascular

invasion (Table 3).⁴⁶ In a meta-analysis of 1,314 women with positive axillary lymph nodes, adjuvant radiotherapy to the chest wall and axilla reduced overall recurrence (RR 0.68; $p=0.00006$) and breast cancer mortality (RR 0.80; $p=0.01$).⁴⁷ Five-year OS varies based on the site of the post-mastectomy LRR after: chest wall (52%), axilla (50%), supraclavicular nodes (28%), chest wall and axilla (28%), and supraclavicular nodes and chest wall or axilla (7%).⁴⁸ When a second surgery is required, the cosmetic outcomes and quality of life are often reduced.

Patients with isolated chest wall recurrences should be evaluated for resection, which are often quite extensive and require complex reconstruction to achieve local control. Approximately 20% experience significant 30-day postoperative morbidity and 5-year OS is 40.8%.⁴⁹ In a randomized trial of 165 patients with post-mastectomy LRR, addition of tamoxifen to surgery and radiotherapy resulted in significantly lower 5-year LRR (10% vs. 28%, $p<0.001$), but similar 5-year OS (74% vs. 76%).⁵⁰ There is no consensus on the management of the axillary nodes in the setting of an isolated LRR within the breast or chest wall in patients who previously underwent SLN biopsy; management should be discussed in a multidisciplinary setting. Patients with axillary nodal LRR who previously underwent SLN biopsy should undergo completion ALND with or without axillary radiotherapy. The role of systemic therapy for LRR has not been the subject of large trials; however, many clinicians treat estrogen-receptor positive disease with tamoxifen, HER2-positive disease with trastuzumab, and hormone receptor negative disease with systemic chemotherapy.⁵¹

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is a primary pleural malignancy arising from mesothelial cells, mostly related to asbestos exposure. In the United States, there are about 3,000 new cases diagnosed each year⁵² with a median OS of only 9–12 months with supportive care alone.⁵³ There are three major histologic subtypes of MPM, with distinctly different outcomes: epithelioid (median OS 20 months), biphasic or mixed (median OS 13 months), and sarcomatoid (median OS 8 months) (HR 1.70; $p<0.0001$).⁵⁴ Other adverse risk factors include lymph node involvement, increased patient age, and non-curative surgery.⁵⁴ The high rate of LRR in MPM is due to its preponderance for diffuse involvement of the serosal surfaces as well as the difficulty in achieving a R0 resection. Morbidity and mortality from MPM is due to LRR, commonly resulting in respiratory compromise, dysphagia, and superior vena cava compression.

The surgical options for MPM are extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). EPP involves en bloc resection of the lung, parietal and visceral pleura, pericardium, and diaphragm, whereas P/D consists of parietal and visceral pleurectomy and resection of diaphragm and/or pericardium if tumor involvement is noted intraoperatively.⁵⁵ P/D is associated with lower perioperative morbidity, similar survival rates, but significantly higher rates of LRR (65% vs. 33%).⁵⁶ Mortality rates are 5–10% for EPP and 3–6% for P/D. Major complications include diaphragm patch dehiscence, bronchopleural fistula, prolonged air leak, chylothorax, and empyema, with over 10% requiring reoperation.⁵⁷

Multiple prospective trials have evaluated heated intraoperative chemotherapy (HIOC). In a phase I/II trial of 44 patients treated with P/D and HIOC (high-dose cisplatin), median OS and DFS were 18 months and 9 months, respectively, but 54% of patients still experienced LRR.⁵⁸ In a phase II trial of 92 patients treated with EPP and HIOC with cisplatin, sodium thiosulfate, and amifostine, the LRR rate was 17%.⁵⁹ However, HIOC increased rates of diaphragmatic patch failure, deep venous thrombosis, atrial fibrillation, and acute respiratory distress syndrome.⁶⁰

Several other less successful intraoperative/perioperative adjuvant therapies have also been evaluated, including heated povidone-iodine (PVP-I), intensity-modulated radiation therapy (IMRT), and photodynamic therapy. The largest reported cohort investigating PVP-I included 102 patients who underwent P/D, hyperthermic PVP-I, chest wall radiotherapy, and systemic chemotherapy, with a median OS of 32 months, overall recurrence rate of 74.5%, and LRR rate of 90%.⁶¹ IMRT plus EPP yielded a 1-year LRR rate of 12%; however, the 1-year OS was only 55%, and 6% of patients experienced fatal (grade 5) pulmonary toxicity.⁶² Lastly, photodynamic therapy is a light-based adjuvant therapy which produces reactive oxygen singlets.⁶³ A 73 patient trial with epithelioid histology receiving photodynamic therapy during P/D reported median OS and DFS of 3 years and 1.2 years, respectively. However, 74% of patients experienced local (+/- distant) recurrence, demonstrating a long interval between disease recurrence and death.⁶⁴

Given the high rates of recurrence, systemic chemotherapy is often employed as part of multimodality treatment regimens for MPM. A phase III trial randomized 456 patients with unresectable MPM to receive single-agent cisplatin or cisplatin plus pemetrexed. The addition of pemetrexed improved response rates (41% vs. 17%, $p < 0.0001$), median progression-free survival (PFS; 5.7 months vs. 3.9 months, $p = 0.001$) and median OS (12.1 months vs. 9.3 months, $p = 0.020$).⁶⁵ Another phase III trial of 448 patients randomized to receive cisplatin and pemetrexed with or without bevacizumab showed that the addition of bevacizumab also increased PFS (9.2 vs. 7.3 months, $p < 0.0001$) and OS (18.8 vs. 16.1 months, $p = 0.017$).⁶⁶ Outcomes of the various treatment options are summarized in Table 4.

Although LRR remains the predominant pattern of failure for MPM patients, there is no standardized treatment approach, with both local and systemic approaches utilized. Isolated chest wall recurrences may be resected, with one series demonstrating median OS was 20.4 months for patients with recurrent epithelioid histology and 7.4 months for those with mixed histology.⁶⁷ Palliative radiotherapy provides short-term symptomatic relief for approximately 4 months.⁶⁸ A recent series of 24 patients with recurrent MPM undergoing 110 cryoablation treatments reported freedom from local recurrence of 91% at 1 year and 74% at 3 years.⁶⁹ Systemic chemotherapy should be considered, particularly for patients with synchronous local and distant recurrence. For recurrent MPM with a malignant pleural effusion, talc pleurodesis and pleural catheter placement are viable palliative options without anti-neoplastic effects. Immunotherapy agents such as pembrolizumab⁷⁰ and nivolumab/ipilimumab⁷¹ reported disease control rates of 72% and 52% in phase I/II trials, respectively; larger trials are needed to further evaluate efficacy.

Non-Small Cell Lung Cancer

Lung cancer is by far the leading cause of cancer death in the United States, accounting for an estimated 154,050 deaths in 2018.¹ Lobar resection is the standard of care for stage I, II, and select III non-small cell lung cancers (NSCLC). However, many patients present with poor baseline pulmonary function, limiting standard treatment options to sublobar resections or radiotherapy for early stage cancers. The oncologic superiority of lobectomy to smaller, non-anatomic resections for NSCLC is supported by multiple studies (Table 5). An early trial randomized 247 patients to lobectomy or limited resection (segmentectomy or wedge resection) demonstrated a tripling of LRR in limited resections ($p=0.008$) with a trend towards lower OS.⁷² A trial with 975 resectable NSCLC patients reported that sublobar resection, stage >IA, squamous or large cell histology, and presence of lymphovascular invasion were independently associated with higher rates of LRR on multivariate analysis.⁷³ Even negative margins after wedge resections, if less than a centimeter, are associated with increased LRR and worse OS rates.⁷⁴ Sublobar resections are associated with higher rates of positive margins (4.0% in wedge, 2.1% in segmentectomy, 1.4% in lobectomy, $p<0.001$), inadequate nodal evaluation (fewer than 4 lymph nodes), and decreased median OS (67.9 months with wedge, 73.7 months with segmentectomy, and 94.5 months with lobectomy; $p=0.0008$).⁷⁵

Stereotactic body radiation therapy (SBRT) is an alternative treatment option to surgery for patients with stage I NSCLC, especially those with medical comorbidities precluding surgery. Phase II trials of early NSCLC report local control rates of 85–92% and OS of 43–60% at 3 years.⁷⁶ Two randomized phase III trials of SBRT versus surgery for operable stage I NSCLC are currently recruiting. Presently, for standard operative risk patients with stage I NSCLC, the American Society of Clinical Oncology does not recommend SBRT outside of a clinical trial.⁷⁷

LRR after surgery for NSCLC primarily occurs in two peaks, the first at 6–8 months and the second at 22–24 months.⁷⁸ Analysis of 74 patients that developed local recurrence after surgery for stage I NSCLC reported that patients who underwent re-resection via surgery survived significantly longer than patients treated with chemotherapy or radiotherapy, though the 5-year post-recurrence survival after repeat surgery remained dismal at only 15%.⁷⁹ In a recent study of 40 patients treated with salvage SBRT for locally recurrent NSCLC deemed inoperable, 18-month OS and local control were 77.6% and 87%, respectively.⁸⁰

Rates of LRR increase with increasing primary stage (5–19% for stage I, 11–27% for stage II and 24–40% for stage IIIA).^{81,82} In a meta-analysis of 2,385 patients, neoadjuvant chemotherapy significantly improved OS (HR 0.87, $p=0.007$), but there was only a trend towards improved local control (HR 0.88, $p=0.20$).⁸³

The location of the recurrence impacts median OS, with LRR (intrathoracic) being 25.5 months vs. distant (extrathoracic) being 10.1 months vs. both at 4.8 months ($p=0.003$).⁸⁴ Patients presenting with an isolated, resectable LRR should be considered for surgery if medically appropriate and other local ablative therapies, such as SBRT, cryoablation, or more standard radiotherapy, if not a surgical candidate. Potential surgical options include

completion lobectomy, pneumonectomy, and chest wall resection. There are no trials directly comparing radiotherapy and surgery for LRR, and therefore it remains unclear which treatment option is superior.^{73,84}

Molecularly targeted agents (i.e. tyrosine kinase inhibitors for EGFR mutated cancer, BRAF inhibitors, ROS1 inhibitors, etc) and immunotherapy agents (pembrolizumab, nivolumab, ipilimumab, atezolizumab, etc) are being used to treat more advanced NSCLC and thus are being used in cases of non-resectable LRR.⁸⁵ Perhaps more importantly are the emerging technologies being developed to prevent LRR in NSCLC, namely more accurate staging using near-infrared lymphatic mapping to more accurately identify SLNs⁸⁶ and the placement of brachytherapy seeds at the staple line following sublobar resections.⁸⁷ Though identifying SLNs is not technically a therapeutic intervention, no LRR occurred in patients with a negative SLN identified using this technique and DFS is superior compared to patients staged with standard lymphadenectomy ($p=0.036$).⁸⁶ The ACOSOG Z4032 phase III trial randomized 222 patients with stage I NSCLC to sublobar resection vs. sublobar resection with brachytherapy seeds placed at the suture line, with a non-significant trend towards decreased local recurrence with brachytherapy in patients with positive staple line cytology (HR 0.22, $p>0.05$).⁸⁷

Retroperitoneal Sarcoma

Soft-tissue sarcomas are malignant mesenchymal tumors with an estimated 12,390 new sarcoma cases and 4,990 deaths in the United States in 2017 with a 5-year OS of 64%.⁸⁸ Approximately 15% of soft-tissue sarcomas arise in the retroperitoneum. Patients often present with large tumors that are characterized by complex anatomic relationships to vital surrounding organs, posing a significant surgical challenge.

The primary pattern of treatment failure for most retroperitoneal sarcomas (RPS) is LRR, and reported 5-year LRR rates range from 26–59%.^{89–91} Death in RPS is typically from direct sequelae of LRR. Completeness of resection, histologic subtype, and tumor grade are the major determinants of survival.^{89,92} Table 6 shows rates of local and distant recurrence for the most common histologic RPS subtypes. Key prognostic factors predictive for LRR are patient age, tumor size, completeness of resection, grade, tumor rupture, multifocality, histologic subtype, and prior radiotherapy.⁹⁰ The predominant RPS histologies are liposarcoma and leiomyosarcoma, with liposarcomas exhibiting the highest rate of LRR.^{90,92} The median OS after LRR is 15–33 months.^{90,93}

A macroscopically complete (R0/R1) resection represents the only potentially curative treatment. Aggressive, multi-visceral organ resections (most commonly kidney and colon, but also occasionally psoas muscle, spleen, diaphragm, abdominal wall muscles, pancreas, and major vessels) are more commonly performed at referral centers.⁹⁰ The ideal extent of resection for RPS is unclear, with some centers advocating complete compartmental resection or liberal en bloc resection of uninvolved organs. Other sarcoma centers recommend limiting organ resection to those with evidence of local invasion or selection of more aggressive surgeries based on histologic subtype (i.e., more aggressive for dedifferentiated liposarcoma).⁹⁴ More extensive surgery at the time of the initial operation is

associated in some but not all series with decreased LRR, though this is still a subject of significant debate as impact on OS is less consistent.^{89,92,95}

Chemotherapy and radiotherapy are used as adjuvant therapies in an attempt to decrease LRR after resection, though their use remains investigational. Doxorubicin, either alone or in combination with ifosfamide, is considered first-line chemotherapy for advanced or metastatic sarcomas but its utility in the adjuvant or neoadjuvant setting for RPS is uncertain.⁹⁶ While radiotherapy may reduce local recurrence, the requirement for large field sizes and the close proximity to radiosensitive organs (i.e., intestines, liver) can result in significant toxicity.⁹⁷ Low rates of local recurrence and reasonable survival rates have been reported in prospective non-randomized trials using preoperative radiotherapy, but these studies were not compared to surgery-alone controls.^{98,99} The results of an international, multi-center, phase III trial enrolling 256 patients evaluating the role of neoadjuvant radiotherapy are expected in 2019. Intraoperative radiotherapy results in 5-year local control rates of roughly 51–83% in retrospective series, but approximately 10% of patients experienced severe gastrointestinal toxicity as well as high rates of neuropathy and ureteral stenosis.¹⁰⁰ An analysis of the SEER database study demonstrated that postoperative radiotherapy showed no survival benefit.¹⁰¹ Regional hyperthermia, in addition to chemotherapy, has been shown to significantly reduce 5-year LRR after macroscopically complete resection (44% vs. 55%, $p=0.044$) but results in similar 5-year OS (57% versus 55%, $p=0.82$).¹⁰² The combination of hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery has been explored, but there is currently no proven efficacy.¹⁰³

The most significant predictor of outcome following a local recurrence is resectability of recurrent disease. Patients most likely to derive benefit from re-resection are those with longer disease-free intervals, no history of tumor rupture at initial operation, low-grade tumors, and unifocal recurrences.⁹⁰ Rates of resectability decrease with each recurrence, from 57% at first local recurrence to 33% at second recurrence and 14% at third recurrence.⁹¹ In borderline resectable recurrences, neoadjuvant chemotherapy or radiotherapy may be utilized in an attempt to downsize the recurrent tumor.^{93,104} However, there is no defined role for chemotherapy for locally recurrent disease, with numerous trials showing no survival benefit for doxorubin-based¹⁰⁵ or second-line⁹⁶ regimens. Immunotherapy studies, including vaccines, checkpoint inhibitor, and adoptive T-cell therapy, are under early-stage investigation.¹⁰⁶

Peritoneal Surface Malignancies

The peritoneum itself can serve as the site of origin for malignancies such as peritoneal mesothelioma and primary peritoneal carcinoma. In addition, appendiceal pseudomyxoma peritonei is a unique condition characterized by peritoneal surface mucinous implants producing gelatinous material, presenting a similar oncologic challenge. Patients with peritoneal surface malignancies frequently die of complications of locoregional disease, most often due to intestinal obstruction. While some patients can be treated with selective removal of gross disease, patients with more diffuse disease often require a more extensive debulking including complete peritonectomy.¹⁰⁷

In addition to cytoreductive surgery (CS), HIPEC is frequently used. Thorough cytoreduction is imperative as the depth of HIPEC drug penetration is estimated to be only 3–5 mm.¹⁰⁸ While the addition of HIPEC seemed to improve OS compared to historic controls, randomized clinical trial data are lacking, and the added benefit of HIPEC to CS at baseline is uncertain.^{109,110} The most common HIPEC regimens use mitomycin C, doxorubicin, taxanes and/or platinum-based chemotherapy.¹⁰⁸ The benefits of locally delivered chemotherapy are particularly evident following treatment of pseudomyxoma peritonei from appendiceal origin, with CS-HIPEC achieving a median OS of 16.3 years and median PFS of 8.2 years in a multi-institutional registry analysis of 2,298 patients.¹¹¹ In this cohort, 51% of patients achieved a complete cytoreduction.¹¹¹ For peritoneal mesothelioma, a meta-analysis of CS-HIPEC reported 84% 1-year survival and 42% OS at 5 years,¹¹² whereas a separate trial using systemic chemotherapy with pemetrexed and cisplatin yielded a 1-year survival of only 57.4%.¹¹³ The median DFS for peritoneal mesothelioma ranged from 7.2 to 40 months.¹¹² Despite this success, the use of HIPEC for PC is associated with significant morbidity and mortality, with mortality rates being 0.9–5.8% (mostly gastrointestinal, pulmonary, and hematologic) of 12–52% being reported even as tertiary centers with significant expertise in these techniques.¹¹⁴

Emerging Therapeutic Drug-Delivery Strategies for Locoregional Recurrence

This review demonstrates that there is a critical unmet need to improve the prevention and treatment of LRR across a number of major malignancies. Fortunately, several novel treatment strategies are emerging to improve local drug delivery to the tumor bed (Figure 2). One appealing approach centers on therapies that can deliver high local doses of chemotherapy with minimal systemic side effects. Such adjuvant treatment options can better target appropriate cell cycle regulators through sustained delivery of high-dose cytotoxic therapy. These novel drug delivery systems fall into two major categories: (1) those intended for intravenous administration and (2) those designed for peritumoral injection or direct implantation into the tumor bed. Anatomic considerations as well as patterns of LRR among different cancers provide insight into the therapeutic strategies that might be most efficacious for a particular patient.

Intravenous delivery of nanoparticle systems, including liposomes, dendrimers, and polymeric nanoparticles are designed to target cancer cells by passive diffusion, conjugation to a specific targeting ligand, or physiologically triggered release, such as pH or temperature.¹¹⁵ Steric stabilization results both in improved efficacy by limiting *in vivo* opsonization in the bloodstream and in resultant increased half-life with fewer systemic side effects. While ligand-targeting has shown enhanced anti-tumor efficacy *in vivo*, its use in clinical studies has thus far been limited by a combination of tumor-dependent physiological barriers and formulation stability.¹¹⁶ Triggering adjuncts have the potential to enhance efficacy in locoregional control. The combination of targeting ligand and heat-triggered release was shown to deliver 3-fold higher intratumoral quantity of chemotherapy drug in an *in vivo* model.¹¹⁷ Targeting mechanisms could allow for higher therapeutic efficacy and decreased off-target toxicity.¹¹⁸

Liposomes contain concentric phospholipid bilayers that enclose a discrete aqueous space, allowing for the delivery of both hydrophobic and hydrophilic compounds. Their biochemical properties can be modified with antibodies, ligands, or other small molecules to allow specific targeting, and their circulation stability and ability to evade the reticuloendothelial system can be prolonged with polyethylene glycol (PEG).¹¹⁶ Although clinical studies of liposomal agents for treatment of LRR are limited, PEGylated liposomal doxorubicin exhibits a better safety profile than non-liposomal doxorubicin and in a phase II trial of elderly and cardiotoxicity-prone patients with high-risk breast cancer, liposomal doxorubicin resulted in a 5-year PFS of 58%.¹¹⁹ While liposomal doxorubicin is the best characterized and most commonly used liposome to date, liposomal formulations of other chemotherapy drugs are being evaluated in clinical trials, including paclitaxel for breast and ovarian cancers and irinotecan for colorectal cancer.

Dendrimers are well-organized, multi-branched macromolecules being investigated for intravenous delivery of drugs, siRNAs, shRNAs, and other therapeutics.¹²⁰ Dendrimers are most commonly derived from polyamidoamine, affording a hydrophilic delivery system. Although no clinical data is available, a pluronic-attached polyamidoamine dendrimer conjugates for doxorubicin successfully overcame multi-drug resistance in *in vitro* and *in vivo* breast cancer models.¹²¹ Further, a folate receptor-targeted dendrimer loaded with an siRNA and cis-diamine platinum exhibits enhanced therapeutic efficacy *in vitro* for lung cancer.¹²² While dendrimers are typically formulated for intravenous delivery, they can also be made in aerosol formulations, providing potential for targeted lung delivery.¹²³

Nanoparticles (NP) are a microscopic delivery system measuring <100 nM in diameter that can be optimized for tumor localization and efficacy by varying their size, shape, or surface charge.¹²⁴ Nanoparticles can be coupled with targeting ligands (i.e., transferrin, LDL, integrin, folate receptor, and epidermal growth factor receptor).¹²⁵ The most well-studied NP example is the clinical use of nanoparticle albumin-bound paclitaxel (nab-pax) for a variety of solid tumor malignancies such as NSCLC, breast, and pancreatic cancers. A phase I trial in advanced NSCLC showed that the combination of radiotherapy, nanoparticle-albumin-bound paclitaxel (nab-PTX) and carboplatin produced an objective response in 71% of patients with acceptable toxicity.¹²⁶ A phase II trial using nab-PTX in 42 patients with recurrent, refractory ovarian cancer reported a 23% response rate, 36% stable disease rate, median OS of 17.4 months, and no grade 4 or higher adverse events.¹²⁷ Polymeric NP are particularly of interest as they can be designed to be responsive to various triggering stimuli, including microenvironmental changes in temperature, pH or hypoxia as well as magnetic or ultrasound activation.¹²⁴ Furthermore, radiotherapy alters the tumor microenvironment immune-cell composition, vasculature, and cell-signaling to enhance intra-tumoral accumulation of NP and the presence of NP may also enhance the efficacy of ionizing radiotherapy.¹²⁸

Our group reported decreased LRR with peritumoral administration of paclitaxel-loaded expansile-nanoparticles (PTX-eNPs) in multiple cancer types. PTX-eNPs delivered intraperitoneally decreased recurrence and improve survival in murine models of peritoneal mesothelioma,¹²⁹ decreased lymph node metastases in a murine breast cancer model,¹³⁰ and demonstrated >20 cm lymphatic migration to the sentinel lymph node in a large animal

model.¹³¹ Interestingly, eNP can be loaded *in vivo* drawing paclitaxel into the tumor, with co-administration of intravenous paclitaxel and local eNPs, resulting in a 5-fold higher intratumoral paclitaxel concentration than intravenous paclitaxel alone.¹³² Another group utilized CD133-targeted paclitaxel nanoparticles and showed significant inhibition of local tumor recurrence in a murine model of CD133-expressing breast cancer.¹³³

An alternative option for the prevention of LRR within the tumor bed is an implantable drug-delivery platform, such as drug-eluting polymer films, wafers, hydrogels, etc. Carmustine-impregnated (Gliadel[®]) wafers improve OS in patients with glioblastoma multiforme and were the first FDA-approved local polymer chemotherapy.¹³⁴ Prolonged local drug delivery through such a platform is an attractive therapeutic option for RPS, rectal cancer, and sublobar resections for NSCLC based on their patterns of LRR. Such local chemotherapy delivery achieves higher drug concentrations than the low drug concentrations achieved at the tumor bed or in regional lymph nodes with systemic therapy.

Local delivery platforms for adjuvant chemotherapy delivery after surgery are being examined, but pose unique challenges. One delivery platform of interest is chemotherapy-eluting polymeric films adhered to collagen-based buttressing material, which allow for flexible surgical fixation and result in sustained, controlled drug release in the resected tumor bed (Figure 3). Paclitaxel-loaded films directly implanted immediately following resection in murine tumor models of lung (LLC) and sarcoma (CS-1) tumors prevented LRR in over 80% of mice for both tumor types.^{134,135} In contrast, only 22.2% of LLC and 11% of CS-1 control mice were free from local recurrence at 60 days, after receiving an equivalent dose of intravenous paclitaxel.^{135,136} While paclitaxel-films led to 50–300 fold higher paclitaxel levels within the local tissues compared to intravenous delivery, systemic paclitaxel levels were minimal, confirming a decreased risk of systemic side effects.¹³⁵ Similarly, a superhydrophobic mesh loaded with cisplatin implanted immediately after surgery also significantly decreased local lung cancer recurrence *in vivo* in a murine model (Figure 4).¹³⁷

Another potential local delivery platform under investigation are hydrogels. Hydrogels are a scaffold of crosslinked hydrophilic polymer chains which form gels when injected *in situ* and can serve as a local drug delivery platform.¹³⁸ A PEG-based hydrogel loaded with paclitaxel significantly decreased LRR in a murine model following resection of a primary breast tumor (9.1% vs. 77.8% with IV paclitaxel).¹³⁹ Recently, a thermosensitive chitosan hydrogel loaded with 5-fluorouracil micelles and cisplatin showed prolonged survival and decreased lung and liver metastases in a mouse model of colorectal peritoneal carcinomatosis.¹⁴⁰ Intrapleural delivery of cisplatin coupled with a fibrin glue showed sustained concentrations of cisplatin at the site of resection 1 week after application during extrapleural pneumonectomy without systemic toxicity in a pig model. This approach is currently under evaluation for mesothelioma in a phase I/II trial.¹⁴¹ Currently in early stages of development, inhalational delivery of multiple nanoparticle subtypes (i.e. polymeric NP, liposomes, polymeric micelles) hold promise for treatment of lung cancers.¹⁴²

While the majority of the above novel drug-delivery platforms remain in pre-clinical testing, the promise of precise tumor-targeting, prolonged therapeutic efficacy, and minimization of

off-target side effects holds significant promise. A keen understanding of patterns of local recurrence inherent in particular tumor subtypes will allow for optimal development and selection of the ideal delivery platform to decrease local recurrence for a given patient (Table 7).

Conclusions

In several of the most common malignancies, local recurrence portends a significantly worse oncologic outcome and quality of life. Remarkable advances in surgical techniques, systemic chemotherapy, and radiotherapy are decreasing locoregional recurrence rates and improving overall survival. However, these therapies are often complicated by significant local and systemic morbidity as well as treatment-related mortality, highlighting the need for better local strategies. Over the next decade, one of the next frontiers to reduce local recurrence, with minimization of systemic side effects, will involve local drug-delivery platforms. Further translational and clinical research is imperative to investigate the safety and efficacy of these various emerging therapeutic strategies.

Acknowledgments

Funding for this research study: NIH R01 EB017722, CA131044–01A1 and CA227433

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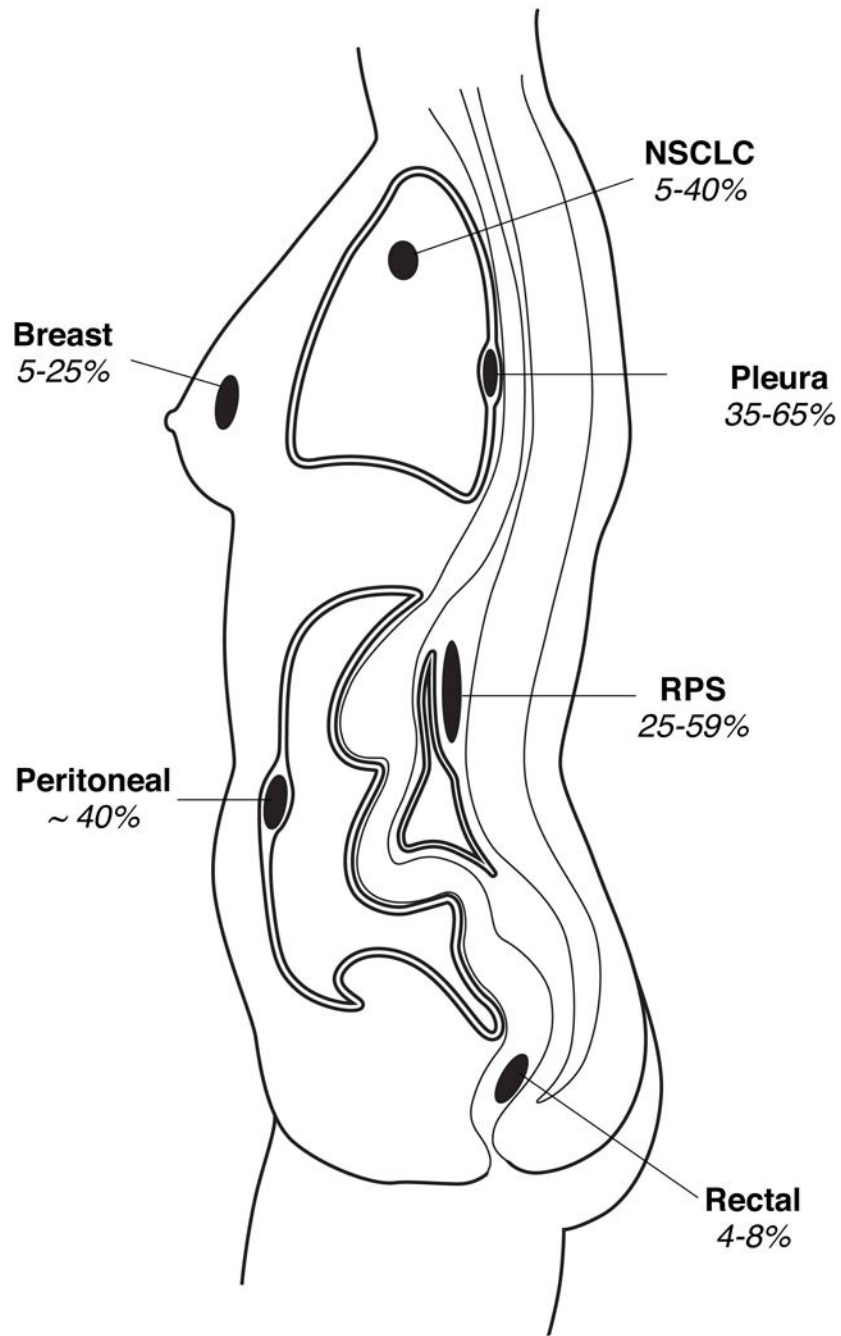


Figure 1.
 A Summary of Local Recurrence Rates for Various Common Malignancies After Surgery.
 3D indicates 3-dimensional; n/a, not applicable.

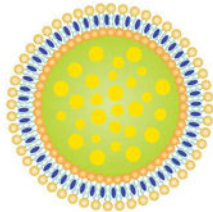

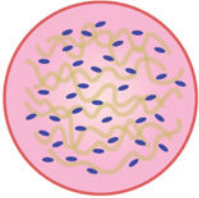
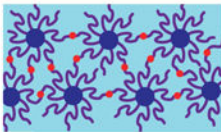
Therapy	Schematic	Description	Size	Advantages	Disadvantages
Liposome		Spherical lipid bilayer nanocarriers	100 to 140 nm	<ul style="list-style-type: none"> Minimal toxicity Improved biodistribution Targeting capability Drug and gene therapy 	<ul style="list-style-type: none"> Lower drug loading capacity Potential for premature drug expulsion
Dendrimer		Symmetric branching monomers from an amine core	10 to 100 nm	<ul style="list-style-type: none"> Bypass efflux transport Cationic charge ideal for gene delivery 	<ul style="list-style-type: none"> Cationic platform results in cell membrane destabilization and hemolysis
Polymeric Nanoparticle		Small particles composed of intertwined polymer backbone	1 to 1000 nm	<ul style="list-style-type: none"> Encapsulates drug and gene therapies Stimuli-responsive Targeting capability 	<ul style="list-style-type: none"> Polymer backbone can cause off-target toxicity Possible rapid drug release
Hydrogel		3D network of crosslinked polymer chains that transform into a gel at body temperature	n/a	<ul style="list-style-type: none"> Able to deliver variety of therapeutics, including nanoparticles and gene therapy Able to have tunable release and prolonged gelation time 	<ul style="list-style-type: none"> Poor adherence to certain tissues based on glycocalyx and other physical properties Potential for non-uniform drug distribution

Figure 2. Leading Novel Drug-Delivery Options in Preclinical and Clinical Testing. NSCLC indicates non-small cell lung cancer; RPS, retroperitoneal sarcoma.

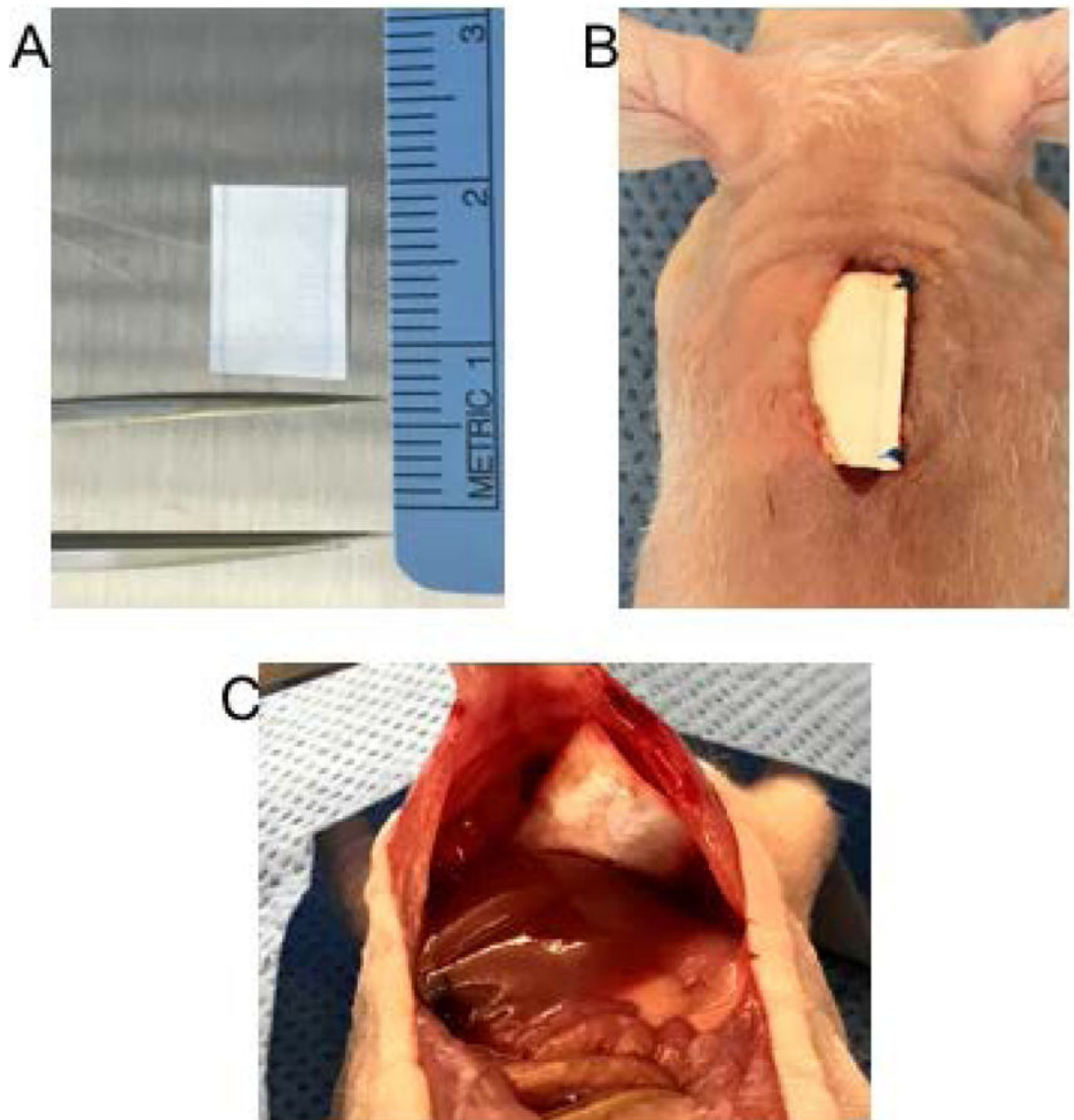


Figure 3. (A) A 1×1 cm Poly(Glycerol Monostearate-Co--Caprolactone) Polymer Mesh, (B) Polymer Mesh Implanted After Subcutaneous Sarcoma Resection With Prolene Suture, and (C) Polymer Mesh Secured to the Diaphragm Superior to the Liver.

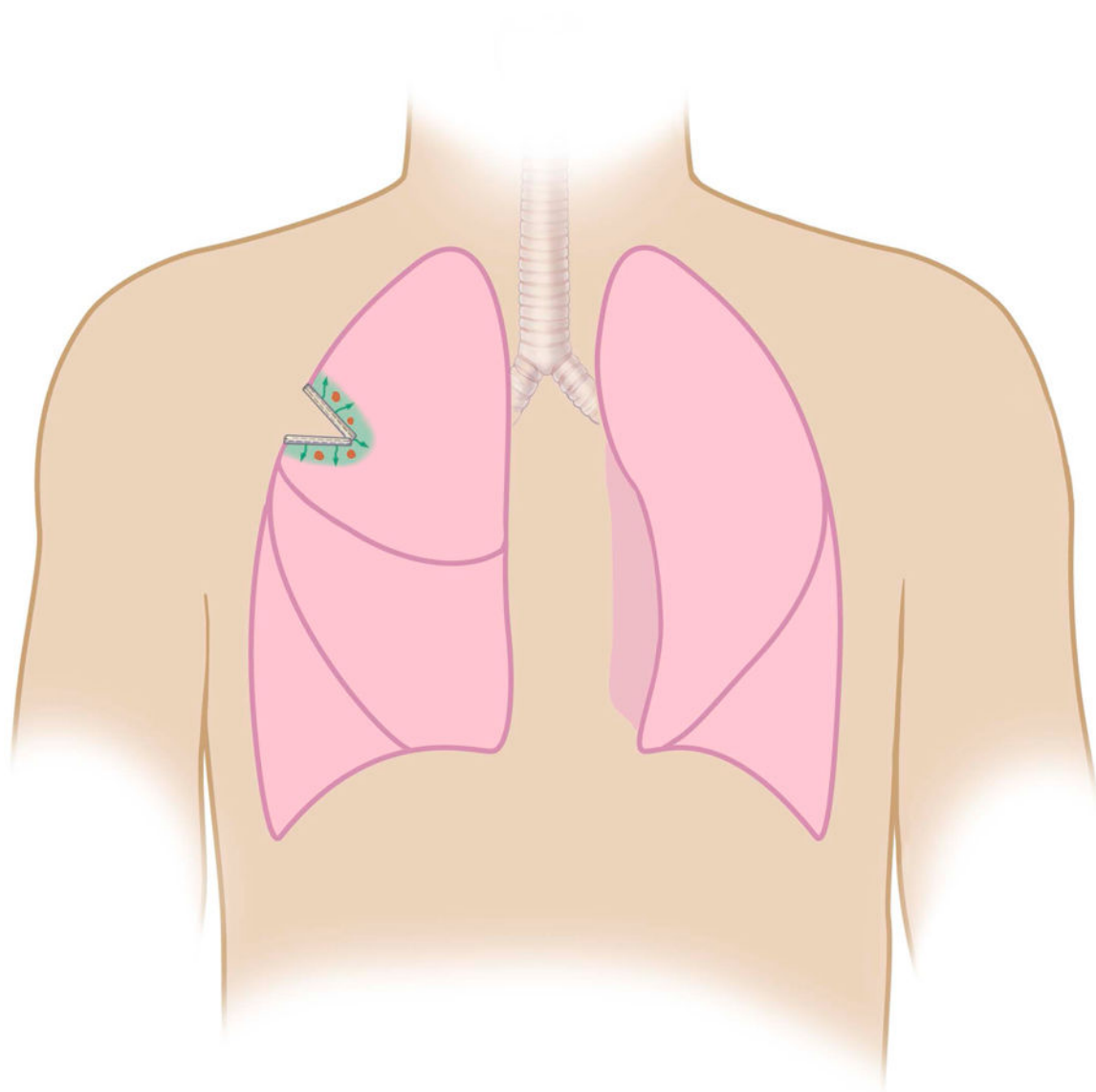


Figure 4.
Polymer Film Containing Cisplatin Can Be Stapled to Lung Tissue During Surgery for Local Drug Delivery.

Table 1.

Currently available and experimental therapies to reduce risk of local recurrence and treat locally recurrent cancer.

Cancer	Treatments to Prevent Local Recurrence	Treatment Options After Local Recurrence	Experimental/Investigational (Phase, if applicable)
Rectal Cancer	<ul style="list-style-type: none"> •Surgery •Neoadjuvant chemotherapy (FOLFOX, FOLFIRI) •Neoadjuvant radiotherapy 	<ul style="list-style-type: none"> •Chemotherapy (FOLFOX, FOLFIRI) •Surgery •Radiotherapy 	<ul style="list-style-type: none"> •Intraoperative radiation therapy •Bevacizumab (II/III) •Cetuximab (II) •Trans-anal excision (III) •Immunotherapy (I/II) •Carbon ion radiation therapy •Aspirin (II), Celecoxib (II)
Breast Cancer	<ul style="list-style-type: none"> •Surgery (mastectomy, lumpectomy) •Chemotherapy •Radiotherapy •Hormonal therapy •Herceptin 	<ul style="list-style-type: none"> •Surgery (mastectomy, radical resection) •Chemotherapy •Radiotherapy •Hormonal therapy •Herceptin 	<ul style="list-style-type: none"> •TKI (III) •Nab-paclitaxel (III) •mTOR inhibitor (III) •Palbociclib (III) •NeuVax vaccine (II) •Cryoablation •Intraoperative radiotherapy •High-intensity focused ultrasound
Mesothelioma	<ul style="list-style-type: none"> •Surgery •Chemotherapy (cisplatin, pemetrexed, gemcitabine) •Radiotherapy 	<ul style="list-style-type: none"> •Surgery •Chemotherapy •Radiotherapy 	<ul style="list-style-type: none"> •Immunotherapy (II) •Photodynamic therapy •Intensity-modulated radiotherapy (I/II) •Heated intraoperative chemotherapy (II)
Non-Small Cell Lung Cancer	<ul style="list-style-type: none"> •Surgery (lobectomy, segmentectomy, wedge) •Chemotherapy •SBRT •Bevacizumab 	<ul style="list-style-type: none"> •Surgical re-resection •Chemotherapy •Radiotherapy •Nab-paclitaxel 	<ul style="list-style-type: none"> •ALK inhibitors (III) •Immunotherapy (III) •TKI (II/III) •Brachytherapy (III)
Retroperitoneal Sarcoma	<ul style="list-style-type: none"> •Surgery •Chemotherapy (doxorubicin, ifosfamide) •Radiotherapy 	<ul style="list-style-type: none"> •Surgery •Radiotherapy •Chemotherapy 	<ul style="list-style-type: none"> •Proton therapy (I/II) •Intraoperative radiotherapy (I/II) •Vaccine therapy (I)
Peritoneal Surface Malignancies	<ul style="list-style-type: none"> •Cytoreductive surgery •HIPEC •Chemotherapy 	<ul style="list-style-type: none"> •Surgery •Chemotherapy •Bevacizumab •PARP inhibitor 	<ul style="list-style-type: none"> •Vaccine therapy (II) •Immunotherapy (II) •mTOR inhibitor (II) •Intraperitoneal NK cells (I)

FOLFOX, leucovorin, 5-fluorouracil, oxaliplatin; FOLFIRI, leucovorin, 5-fluorouracil, irinotecan; TKI, tyrosine kinase inhibitor; Nab, nanoparticle-albumin bound; mTOR, mammalian target of rapamycin; SBRT, stereotactic body radiation therapy; ALK, anaplastic lymphoma kinase; HIPEC, hyperthermic intraperitoneal chemotherapy; PARP, poly (ADP-ribose) polymerase

Table 2.

Local recurrence rates in rectal cancer associated with either more extensive surgery or after neoadjuvant radiotherapy, based on randomized trials data

Clinical Trial	Treatment Group (number of patients)	Local Recurrence Rate	p-value
Japanese Trial ⁸	Mesorectal excision alone (350)	17.6% (5-year)	p=0.024
	Mesorectal excision plus lateral lymph node dissection (351)	9.8% (5-year)	
Dutch TME Trial ¹¹	TME alone (701)	11.0% (5-year)	p<0.001
	Preoperative radiotherapy plus TME (713)	4.6% (5-year)	
MRC CR07 Trial ¹²	TME with selective postoperative chemoradiotherapy (676)	10.6% (3-year)	p<0.0001
	Preoperative radiotherapy plus TME (674)	4.4% (3-year)	

TME, total mesorectal excision

Table 3.

Major significant risk factors for developing locoregional recurrence in breast cancer patients

Primary Risk Factors for Locoregional Recurrence in Breast Cancer
Primary tumor size over 4 cm
4 or more positive axillary lymph nodes
Lack of radiotherapy treatment
Younger age
Negative hormone receptor status
Lymphovascular invasion

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Table 4.

Outcomes associated with various treatment options for patients with locally recurrent malignant pleural mesothelioma

Treatment	Locoregional Recurrence	Survival	Complications
Supportive Care	n/a	Median OS 9–12 mo	n/a
Extrapleural Pneumonectomy	33–42% (site of first recurrence)	Median OS 12–32 mo	5–10% perioperative mortality
Pleurectomy/Decortication	53–65% (site of first recurrence)	Median OS 12–26 mo	3–6% perioperative mortality
Heated Intraoperative Chemotherapy	17–54% (site of first recurrence)	Median OS 12–26 mo	Increased rates of diaphragmatic patch failure, DVT, ARDS, and atrial fibrillation
Systemic Chemotherapy	Median PFS 5.7–10 mo	Median OS 12.1–29.1 mo (if extrapleural pneumonectomy + radiotherapy completed)	27.2% grade III or higher complications
Heated Povidone-Iodine	Median PFS 12 mo (89.5% local-first recurrence)	Median OS 32 mo (with pneumonectomy/decortication, radiation therapy, and adjuvant chemo)	Persistent air leak, chylothorax, pneumonia, empyema, ARDS
Intensity Modulated Radiation Therapy	12% at 1 year	1-year OS 55%	6% fatal pulmonary toxicity
Photodynamic Therapy	Median PFS 9.6 mo	Median OS 15–31.7 mo (with surgery)	Skin burning, pain, cellulitis

OS, overall survival; PFS progression free survival; DVT, deep venous thrombosis; ARDS, acute respiratory distress syndrome

Table 5.

Outcomes associated with various treatment options for patients with locally recurrent early stage non-small cell lung cancer

Treatment		Locoregional Recurrence	Positive Margin Rate
Surgery	Lobectomy	4.9–7%	1.4%
	Segmentectomy	9.1–16%	2.1%
	Wedge resection	11–27.8%	4.0%
Stereotactic body radiotherapy ^a		8–15%	n/a

^aOnly includes early stage non-small cell lung cancers

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Table 6.

Rates of local and distant recurrence in the most common histologic subtypes of retroperitoneal sarcoma

Retroperitoneal Sarcoma Histologic Subtype	Overall Percentage of Patients	Local Recurrence Rate	Distant Recurrence Rate
Dedifferentiated liposarcoma	30–40%	40–85%	10–20%
Well-differentiated liposarcoma	25–30%	5–45%	0–5%
Leiomyosarcoma	15–25%	10–30%	40–50%
Malignant peripheral-nerve sheath tumor	2–5%	35–65%	40–70%
Solitary fibrous tumor	2–5%	5–10%	20–30%

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Table 7.

Ideal deal drug delivery platforms based on patterns of locoregional recurrence

Cancer	Ideal Novel Drug Delivery Platform
Rectal Cancer	<ul style="list-style-type: none"> •Nanoparticle (intravenous or intraperitoneal) •Hydrogel at anastomosis •Polymer film along pelvic side wall
Breast Cancer	<ul style="list-style-type: none"> •Nanoparticle (intravenous or peritumoral) •Polymer film in resection bed
Mesothelioma	<ul style="list-style-type: none"> •Intrapleural nanoparticle •Polymer film (after pneumonectomy/decortication)
Non-Small Cell Lung Cancer	<ul style="list-style-type: none"> •Polymer film along staple line •Systemic nanoparticle/dendrimer/liposome
Retroperitoneal Sarcoma	<ul style="list-style-type: none"> •Polymer film in resection bed
Peritoneal Surface Malignancies	<ul style="list-style-type: none"> •Intraperitoneal nanoparticle

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