REVIEW

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Precision Medicine and Artificial Intelligence in Next-Generation Cancer Surgery: A Comprehensive Analysis of Clinical Applications, Therapeutic Outcomes, and Implementation Strategies

Alireza Negahi[1], Mehdi Khosravi-Mashizi[1,2]*, Hossein Najdsepas[1], Hossein Negahban[1], Seyede Arefe Mousavi-Beni[3], Reza Shahrokhi Damavand[4], Amirhosein Naseri[5], Fatemeh Jayervand[6], Amirhossein Shahbazi[7], Amirhossein Rahmani[8], Hossein Neamatzadeh[9]

Abstract

Background: Cancer surgery is undergoing transformative integration of precision medicine, artificial intelligence (AI), robotics, advanced imaging, and molecular technologies. These innovations promise enhanced surgical precision, improved patient outcomes, and personalized treatment approaches through data-driven decision-making. **Methods:** A comprehensive systematic literature review was conducted across PubMed, Embase, Cochrane Library, and Web of Science databases from January 2020 to November 2025. Studies were analyzed for clinical applications, therapeutic outcomes, cost-effectiveness, and implementation challenges. Primary endpoints included surgical accuracy, margin status, survival outcomes, complication rates, and technology adoption metrics. **Results:** Precision medicine utilizing genomic profiling and circulating tumor DNA demonstrated 94.9% sensitivity and 88.8% specificity in multi-cancer detection. The CIRCULATE-Japan GALAXY study showed ctDNA positivity during the molecular residual disease window predicted significantly inferior disease-free survival (HR 11.99; $P < 0.0001$) and overall survival (HR 9.68; $P < 0.0001$). AI-assisted surgical systems achieved area under the curve values of 0.76–0.85 in outcome prediction and reduced surgical complications by 25–30%. The da Vinci 5 robotic system demonstrated 43% reduction in tissue damage through force feedback technology. Meta-analysis of 15,137 patients showed robotic pancreatoduodenectomy reduced hospital stays and conversion rates compared to laparoscopy. Fluorescence-guided surgery achieved improved 5-year overall survival (80.6% vs. 66.7%, $P = 0.018$) in gastric cancer. Mass spectrometry techniques achieved 93.4–97.1% diagnostic accuracy. Perioperative immunotherapy in non-small cell lung cancer reduced recurrence risk by 43% (HR 0.57) and improved pathological complete response rates over 5-fold (RR 5.58). Nanotechnology-based delivery systems reduced cardiac toxicity (6% vs. 21%) while maintaining therapeutic efficacy. **Conclusions:** The convergence of precision medicine, AI, robotics, and molecular technologies is revolutionizing cancer surgery toward personalized, data-driven interventions with substantial clinical outcome improvements. Implementation challenges including cost, standardization, and healthcare disparities require systematic addressing for widespread adoption.

Keywords: Cancer Surgery- Precision Medicine- Artificial Intelligence- Robotic Surgery- Liquid Biopsy

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Introduction

Cancer remains a leading global health challenge, with 2,041,910 new cases and 618,120 cancer-related deaths projected in the United States for 2025, representing a persistent burden despite technological advances [1]. The cancer mortality rate has declined by 34% since 1991, averting nearly 4.5 million deaths through smoking reductions, earlier detection for some cancers, and improved treatment strategies [1, 2]. Surgical resection

*[1]Breast Health & Cancer Research Center, Iran University of Medical Sciences, Tehran, Iran. [2]Department of General Surgery, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [3]Afshar Hospital Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [4]Urology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran. [5]Department of Colorectal Surgery, Imam Reza Hospital, AJA University of Medical Sciences, Tehran, Iran. [6]Department of Obstetrics and Gynecology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [7]Student Research Committee, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran. [8]Department of Plastic Surgery, School of Medicine, Iranshahr University of Medical Sciences, Iranshahr, Iran. [9]Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. *For Correspondence: mkhosravi.mas@gmail.com*

continues as the primary curative treatment modality for 60–70% of solid tumors, yet challenges including incomplete margin clearance affecting 10–40% of patients, postoperative morbidity, and disease recurrence continue to limit optimal therapeutic outcomes [2]. The integration of precision medicine, AI, robotics, advanced imaging, and molecular technologies is fundamentally transforming cancer surgery toward data-integrated, personalized interventions with measurable clinical improvements [3, 4].

The transformative impact of precision medicine is evidenced by clinical studies demonstrating that comprehensive molecular tumor profiling achieves significantly improved survival outcomes in patients with advanced solid tumors. The ROME Trial, a phase II multicenter study of 1,794 patients with advanced solid tumors, demonstrated that patients receiving tailored therapy based on concordant tissue and liquid biopsy results achieved a significantly higher overall response rate (17.5% vs. 10.0%; P = 0.029) and improved overall survival (11.05 vs. 7.70 months) compared to standard of care [5, 6]. The concordance rate between tissue and liquid biopsies was 49%, with the addition of liquid biopsy increasing detection of actionable alterations by over 60% [6]. Simultaneously, AI applications in surgical settings have demonstrated remarkable potential, with machine learning models achieving greater than 85% accuracy in predicting patient outcomes, surgical complications, and treatment response patterns across multiple oncological specialties [7, 8].

The emergence of liquid biopsy technologies utilizing ctDNA analysis has revolutionized perioperative cancer monitoring, with the TriOx multi-cancer detection test demonstrating 94.9% sensitivity and 88.8% specificity across six cancer types including colorectal, esophageal, pancreatic, renal, ovarian, and breast cancers, enabling earlier intervention at more curable disease stages [9, 10]. Advanced imaging modalities including fluorescence-guided surgery achieve greater than 95% specificity in tumor delineation, while mass spectrometry-based intraoperative margin detection demonstrates greater than 95% diagnostic accuracy [11–13]. Contemporary cancer surgery is evolving toward an integrated paradigm encompassing preoperative molecular characterization, AI-enhanced intraoperative guidance, robotic precision platforms, and postoperative surveillance through advanced liquid biopsy technologies. The objective of this review is to provide comprehensive analysis of these advanced technologies and their integration potential in modern cancer surgery practice.

Materials and Methods

Literature Search Strategy

A comprehensive systematic literature review was conducted to identify relevant studies evaluating precision medicine, AI, robotics, and advanced technologies in cancer surgery. Electronic searches were performed systematically across multiple complementary databases from January 2020 to November 2025, including primary biomedical databases such as PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science Core Collection. Specialized databases including CINAHL Plus, PsycINFO, BIOSIS Citation Index, Scopus, and CAB Direct were also consulted. Grey literature sources comprising clinical trial registries like ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and EU Clinical Trials Register were searched alongside conference proceedings from major oncological societies and regulatory documents from the FDA and EMA. The search strategy incorporated comprehensive combinations of Medical Subject Headings terms and free-text keywords following established PICO framework principles, encompassing core concepts including precision medicine, AI, robotic surgery, and genomic profiling.

Study Selection Criteria

Inclusion criteria comprised peer-reviewed articles published in English language; clinical studies encompassing randomized controlled trials, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, systematic reviews, and meta-analyses; human subjects diagnosed with solid malignancies undergoing surgical intervention; and studies evaluating precision medicine technologies, AI applications, machine learning algorithms, robotic surgical platforms, advanced imaging modalities, molecular diagnostic techniques, or nanotechnology applications specifically within surgical oncology contexts. Studies were required to report quantitative clinical outcomes including overall survival, disease-free survival, progression-free survival, recurrence rates, surgical performance metrics, diagnostic accuracy measures, quality of life assessments, or comprehensive cost-effectiveness analyses. A minimum sample size of 30 patients was required for observational clinical studies. Exclusion criteria systematically eliminated preclinical studies, in vitro experiments, animal model studies, or computational modeling studies without direct clinical validation, as well as case reports and opinion pieces lacking empirical data.

Data Extraction

Comprehensive data extraction was systematically conducted using standardized, pre-piloted extraction forms developed specifically for this review to encompass study characteristics, detailed patient demographics, intervention specifications, clearly defined primary and secondary endpoints with validated outcome measures, statistical methodologies employed, quantitative clinical outcomes reported with confidence intervals and effect sizes, comprehensive safety profiles, and economic evaluations. Two independent reviewers conducted systematic screening of titles and abstracts followed by full-text assessment using standardized, pretested data extraction forms, ensuring consistency and minimizing extraction errors through parallel independent extraction processes. Inter-reviewer agreement was assessed using Cohen's kappa coefficient, with disagreements resolved through structured consensus discussion.

Precision Medicine Applications in Surgical Oncology
Genomic Profiling and Biomarker-Guided Surgery

Next-generation sequencing has emerged as fundamental for precision oncology, enabling identification of genetic mutations influencing tumor behavior and treatment responses across diverse malignancy types. Comprehensive genomic profiling studies utilizing whole-exome sequencing reveal that approximately 67% of cancer patients harbor actionable molecular targets detectable through comprehensive genomic profiling, significantly higher than traditional small-panel tests [14]. Patients matched to targeted therapies or immunotherapies based on comprehensive genomic profiling results show improved overall survival, with biomarker-guided targeted therapy achieving hazard ratios of 0.66 (95% CI, 0.52 to 0.84) compared to chemotherapy alone [15].

The ROME Trial demonstrated that patients receiving tailored therapy had a significantly improved overall response rate compared to standard of care (17.5% vs. 10.0%, P = 0.029), with time to treatment failure extended from 2.8 to 3.5 months [5, 6]. Furthermore, the superior outcomes observed in patients with concordant biopsy findings highlight the potential of combined molecular profiling approaches to optimize patient selection for tailored therapies [6].

Recent advances include DeepHRD, an AI-powered tool for detecting homologous recombination deficiency in tumor samples. DeepHRD predicted homologous recombination deficiency with an area under the curve of 0.81 (95% CI, 0.77–0.85) for breast cancer and classified 1.8-fold to 3.1-fold more patients as homologous recombination deficiency positive than standard molecular tests, with significant survival differences observed in platinum-treated patients [16, 17]. In colorectal cancer management, mutations in critical genes including APC, TP53, and KRAS demonstrate significant correlation with clinical outcomes and tumor regression grades following neoadjuvant therapy, with molecular profiling guiding optimal surgical timing and extent determination [18]. The comprehensive performance metrics of precision medicine technologies are detailed in Table 1.

Table 1. Precision Medicine Technologies and Clinical Outcomes

Technology	Primary Application	Sensitivity	Specificity	Clinical Impact	Key Evidence	References
Genomic profiling (NGS)	Biomarker identification	95–98%	92–96%	ORR 17.5% vs 10.0%; P<0.029 with matched therapy	ROME Trial	5,6,14,15
DeepHRD (AI tool)	Homologous recombination deficiency detection	AUC 0.81	90–95%	1.8–3.1-fold increase in HRD detection; improved platinum response	Bergstrom et al.	16,17
Circulating tumor DNA	Minimal residual disease detection	90%	85–92%	ctDNA positivity associated with HR 11.99 for DFS and 9.68 for OS	CIRCULATE-Japan GALAXY	19,20
Tumor mutational burden	Immunotherapy selection	80–90%	75–85%	17–25.3% absolute pCR improvement with perioperative immunotherapy	Phase III trials	14,21–23
TriOx multi-cancer test	Early multi-cancer screening	94.90%	88.80%	Detection of six cancer types; ctDNA fraction limit 0.7%	Vavoulis et al.	9,10
Shield blood test	Colorectal cancer screening	83%	90%	First FDA-approved blood-based CRC screening assay	ECLIPSE Trial	24,25

Abbreviations: NGS, next-generation sequencing; ORR, overall response rate; HRD, homologous recombination deficiency; AUC, area under the curve; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response; ctDNA, circulating tumor DNA; CRC, colorectal cancer; FDA, Food and Drug Administration.

Liquid Biopsy and ctDNA Applications

Liquid biopsy technologies, particularly ctDNA analysis, have revolutionized perioperative cancer management through non-invasive monitoring capabilities [20]. Blood remains the most studied biofluid, with ctDNA as the predominant analyte, followed by circulating tumor cells and extracellular vesicles, with publications on liquid biopsy in solid tumors doubling since 2020, highlighting its expanding clinical utility [24-26]. Clinical studies demonstrate that postoperative ctDNA detection precedes conventional imaging changes by 3–6 months, enabling earlier recurrence detection with greater than 90% sensitivity in appropriately selected cases [27].

The CIRCULATE-Japan GALAXY observational study, one of the largest prospective studies of ctDNA testing in resectable colorectal cancer with 2,518 patients analyzed, demonstrated the prognostic value of ctDNA positivity during the molecular residual disease window with significantly inferior disease-free survival (DFS) (HR 11.99; 95% CI, 12.59–19.68; P < 0.0001) and overall survival (OS) (HR 9.68; P < 0.0001) [19, 20]. Among

patients who were ctDNA positive and received adjuvant therapy, 72.9% achieved ctDNA clearance, and sustained ctDNA clearance was associated with remarkably better outcomes compared to transient clearance (HR 32.57; 95% CI, 9.94–106.76; P < 0.0001) [19]. Furthermore, a 50% or greater decrease in ctDNA levels at 6 months was associated with better DFS compared to patients with less than 50% decrease or increase in ctDNA levels (HR 2.39; 95% CI, 1.32–4.34; P = 0.004) [20]. The TriOx blood test, developed using machine learning algorithms at the University of Oxford, represents a significant advancement in multi-cancer early detection, demonstrating 94.9% sensitivity and 88.8% specificity across six cancer types [9, 10]. Using whole-genome TET-Assisted Pyridine Borane Sequencing (TAPS) combined with machine learning, the test can detect cancers even at early stages and distinguish between people who have cancer and those who do not [10]. The FDA approval of the Shield blood test for colorectal cancer screening on July 29, 2024 marks a major milestone in the clinical translation of liquid biopsy technology, representing the first blood test approved by the FDA as a primary screening option for colorectal cancer [24, 25]. Based on the ECLIPSE trial involving more than 20,000 patients, Shield demonstrated 83% sensitivity for colorectal cancer detection with 90% specificity for advanced neoplasia [24].

Tumor Molecular Classification and Immunogenomics

Tumor mutational burden quantification and microsatellite instability status increasingly inform perioperative immunotherapy integration strategies. Neoadjuvant immunotherapy administration prior to surgical resection demonstrates significant efficacy in tumor downstaging, with pathological complete response rates of 17–25.3% depending on tumor type and molecular characteristics [21–23]. The integration of biomarker-guided patient selection substantially enhances perioperative immunotherapy efficacy while reducing unnecessary toxicity exposure.

The SCORPIO machine learning system, utilizing routine blood test parameters from 9,745 immune checkpoint inhibitor-treated patients across 21 cancer types, achieved median AUC values of 0.763 for overall survival prediction at multiple time points, significantly outperforming traditional biomarkers including tumor mutational burden (median AUC values 0.503–0.543) and *PD-L1* expression levels [28, 29]. Additionally, SCORPIO demonstrated superior predictive performance for predicting clinical benefit, with AUC values of 0.71 and 0.64, compared to tumor mutational burden [28, 29].

Artificial Intelligence and Machine Learning Integration
Preoperative Planning and Risk Stratification

AI applications in preoperative planning demonstrate remarkable accuracy in patient stratification and clinical outcome prediction across surgical oncology disciplines. Advanced AI algorithms analyzing comprehensive electronic health records, multimodal imaging data, and genomic profiles achieve AUC values of 0.91–0.96 in predicting surgical outcomes, postoperative complications, and long-term survival patterns [7, 30]. A 2025 systematic review of AI integration into robotic oncologic surgery demonstrated that AI significantly supports various stages of cancer surgery, including preoperative planning for estimating conversion risk and intraoperative tumor localization [8].

AI-powered diagnostic tools achieve greater than 96% accuracy in breast cancer detection, 87% sensitivity and specificity in lung cancer identification, and 97% sensitivity with 95% specificity in colorectal cancer screening applications [31]. Recent developments include foundation AI models that predict postoperative complications from clinical notes with remarkable accuracy. A study analyzing 84,875 surgical notes demonstrated that specialized large language models correctly identified 33–39 additional patients per 100 who experienced postoperative complications compared to traditional natural language processing methods [32].

Another landmark study demonstrated that AI models combining electrocardiogram data with patient medical records achieved 85% accuracy in predicting post-surgical complications including heart attack, stroke, or death within 30 days after surgery, significantly outperforming current risk scores that achieve approximately 60% accuracy. The system analyzed preoperative ECG data from 37,000 patients, with the "fusion" model combining ECG information with medical record details demonstrating superior predictive performance [33].

Intraoperative AI Applications and Real-Time Decision Support

Intraoperative AI applications provide real-time surgical guidance through advanced image analysis and anatomical structure identification (Table 2). A comprehensive systematic review involving multiple studies demonstrated that AI significantly improved complication prediction accuracy by 25% over traditional methods and reduced intraoperative errors [34]. AI-assisted surgeries showed an average reduction of approximately 30 minutes in surgical time in complex cases, with a relative reduction in postoperative adverse events (relative risk 0.85) [34, 35].

AI-enhanced fluorescence imaging systems enable precise tumor margin delineation with greater than 95% specificity rates, significantly reducing positive surgical margin rates [36]. Computer vision systems utilizing deep learning architectures demonstrate superior performance in tissue classification compared to traditional histopathological methods, achieving greater than 90% accuracy in intraoperative frozen section analysis while reducing decision-making time from 20–30 minutes to 2–5 minutes [37, 38]. The integration of AI with robotic surgery platforms enables autonomous task performance and enhanced surgical precision [39].

Implementation Challenges and Clinical Integration

Despite promising results, AI integration faces significant challenges including data standardization requirements, algorithm interpretability concerns, and regulatory approval processes. Data quality limitations and availability constraints, particularly in smaller healthcare

institutions, restrict widespread implementation and equitable access to advanced technologies [40]. Algorithm bias concerns require attention to ensure equitable clinical outcomes across diverse patient populations. Clinical workflow integration requires substantial infrastructure investments, comprehensive staff training programs, and organizational culture changes [41].

Robotic-Assisted Surgery: Clinical Applications and Outcomes

Clinical Outcomes and Surgical Precision

Robotic-assisted surgery has revolutionized cancer treatment through enhanced precision and minimally invasive approaches. The landmark REAL trial, a multicenter randomized controlled trial of 1,171 patients with middle or low rectal cancer, demonstrated that robotic surgery achieved significantly lower 3-year locoregional recurrence (1.5% vs. 4.0%, P = 0.025) and higher 3-year disease-free survival (87.3% vs. 83.6%, P = 0.035) compared to laparoscopic surgery [42, 43]. Comprehensive analysis of robotic platforms shows 35–50% reduction in intraoperative blood loss, 25–30% decrease in hospital stays, and 60–70% lower conversion to open surgery rates compared to conventional laparoscopic approaches [44, 45].

Expanding beyond colorectal applications, a 2025 meta-analysis of 29 studies including 15,137 patients evaluating robotic pancreatoduodenectomy versus laparoscopic approaches demonstrated that robotic surgery significantly reduced the conversion rate to open surgery (RR 0.47) and shortened hospital stays, with no increase in mortality or fistula rates. The introduction of the da Vinci 5 surgical system represents a significant technological leap, incorporating force feedback technology that allows surgeons to "feel" tissue tension [47]. Clinical evaluations indicate this technology reduces force exerted on tissue, resulting in up to 43% less tissue damage during procedures, which may translate to faster recovery times. Furthermore, a one-year analysis of da Vinci 5 in robotic thoracic surgery from Ohio State University demonstrated that force feedback technology is associated with significantly reduced average and peak instrument forces during procedures, particularly at medium and high sensitivity settings [48].

In colorectal cancer, robotic procedures demonstrate significantly lower conversion rates in challenging scenarios including obese patients (odds ratio 0.41), male patients (odds ratio 0.28), and complex rectal cases (odds ratio 0.10) [49]. A 2025 study comparing robotic versus 3D laparoscopic resection for rectal cancer found that robotic surgery was an independent predictor of improved urinary function recovery at 3 months (OR 3.45; 95% CI, 1.82–6.54; P < 0.001) and enhanced sexual function recovery at 6 months [50].

Economic Considerations and Cost-Effectiveness

Robotic surgery implementation involves substantial costs: $1–2.5 million initial investment plus $150,000–200,000 annual maintenance, yet comprehensive analyses demonstrate favorable long-term economics [51, 52]. Quality-adjusted life year (QALY) gains were statistically

Table 2. Artificial Intelligence Applications and Performance Metrics

AI system / application	Technology platform	Accuracy / AUC	Clinical outcomes	Validation level	References
SCORPIO prediction system	Machine learning	AUC 0.763	Superior prediction of immunotherapy benefit vs TMB and PD-L1	Multi-institutional cohort (n=9,745)	28,29
DeepHRD detection	Deep learning	AUC 0.81	≈3-fold higher HRD identification vs genomic assays; improved platinum response	External validation cohorts	16,17
Preoperative risk stratification models	Multimodal integration (EHR, imaging, genomics)	AUC 0.91–0.96	25–30% reduction in postoperative complications	Prospective and retrospective clinical validation	7,30
Postoperative complication prediction	ECG–clinical data fusion model	85% accuracy	Outperforms conventional risk scores (~60% accuracy)	Single-center cohort (n≈37,000)	33
Foundation LLM for surgery	Large language model	33–39% relative improvement	More accurate identification of patients with postoperative complications from clinical notes	Surgical note corpus (n=84,875)	32
AI integration in robotic surgery	AI-enhanced robotic platforms	Not applicable (process metric)	Improved complication prediction; ≈30-minute reduction in operative time in complex cases	Systematic review and pooled evidence	8,34,35

Abbreviations: AI, artificial intelligence; AUC, area under the curve; TMB, tumor mutational burden; *PD-L1*, programmed death-ligand 1; EHR, electronic health record; ECG, electrocardiogram; LLM, large language model.

significant for robotic surgeries (mean difference 0.01), with incremental cost-effectiveness ranging from $14,925–28,860 per QALY, below commonly accepted thresholds of $50,000 [51, 52]. Studies focusing on older patients reported incremental cost-effectiveness ratios of $28,860 per QALY with 82.2% cost-effectiveness probability [51]. A cost-utility analysis comparing robot-assisted radical prostatectomy to laparoscopic radical prostatectomy showed an incremental cost-utility ratio of €34,206 per QALY gained; when robotic surgery is centralized, the incremental cost-utility ratio decreased to €3,495 per QALY gained [53].

Future Technological Developments

Next-generation robotic systems integrate sophisticated AI capabilities for autonomous task performance and enhanced surgical precision. AI-driven robotic systems offer an unprecedented combination of enhanced precision, real-time decision support, and minimally invasive capabilities, enabling surgeons to visualize tumor margins more effectively and achieve higher consistency in complex oncologic procedures [8, 39]. Newer systems like the hinotori surgical robot system are showing comparable short-term outcomes to established platforms in rectal cancer surgery, indicating a competitive future landscape [54].

Advanced Imaging and Fluorescence-Guided Surgery
Clinical Applications and Diagnostic Accuracy

Fluorescence-guided surgery enables real-time tumor visualization and precise margin delineation during surgical procedures. The FUGES-012 randomized clinical trial, evaluating long-term outcomes of indocyanine green (ICG) fluorescence imaging-guided laparoscopic lymphadenectomy for gastric cancer, demonstrated that fluorescence-guided surgery significantly improved 5-year overall survival (80.6% vs. 66.7%, P = 0.018) and reduced the cumulative incidence of all-cause death (HR 0.61, P = 0.045) compared to conventional lymphadenectomy [11, 55]. ICG-guided lymphadenectomy not only significantly improved the 5-year OS and DFS but also noticeably reduced the cumulative incidence of early recurrence [55].

Emerging targeted fluorophores are expanding the utility of this technology to pediatric oncology. A 2025 study identified that folate receptor beta is expressed in 100% of pediatric solid tumor samples, including osteosarcoma and Wilms tumor, suggesting that folate-targeted dyes like pafolacianine could serve as tumor-agnostic imaging agents for pediatric cancer surgery [56]. ICG, the most validated fluorescent agent, demonstrates greater than 90% accuracy in tumor boundary identification across cancer types [57]. A meta-analysis examining fluorescence-guided hepatectomy demonstrated that this approach can effectively increase the R0 resection rate and may contribute to reducing postoperative recurrence of liver cancer [58]. In bladder cancer surgery, fluorescence imaging-guided radical cystectomy with pelvic lymph node dissection significantly improved lymph node localization accuracy and reduced operating time [59].

Research at Vanderbilt University Medical Center demonstrated that combining in vivo and ex vivo fluorescence imaging data significantly improves surgical margin achievement in head and neck cancer, with fluorescent areas associated with margins averaging 2.6 mm compared to 6.9 mm for non-fluorescent areas [60]. As detailed in Table 3, fluorescence-guided surgery achieves tumor delineation accuracy greater than 95% with significant improvements in oncological outcomes.

Integration with AI and Advanced Analytics

AI integration with fluorescence imaging provides real-time quantitative analysis and automated tumor boundary delineation. Machine learning models analyzing fluorescence patterns achieve greater than 90% accuracy in tissue classification, enabling evidence-based surgical decision-making support and reducing subjective interpretation variability [36, 37]. Multimodal imaging approaches combining fluorescence, Raman spectroscopy, and hyperspectral imaging provide comprehensive tissue characterization capabilities [67]. Incorporating AI helps enhance fluorescence imaging and is poised to bring major innovations to surgical guidance, thereby realizing precision cancer surgery [68].

Mass Spectrometry-Based Intraoperative Analysis
Rapid Evaporative Ionization Mass Spectrometry (REIMS)

REIMS technology analyzes tissue chemical profiles from electrosurgical smoke, enabling real-time classification during surgical procedures. A systematic review analyzing 26 studies demonstrated REIMS application across eight surgical specialties with promising results regarding accuracy, sensitivity, and specificity for tissue identification [12]. Clinical studies demonstrate exceptional diagnostic accuracy: 93.4% sensitivity and 94.9% specificity in breast cancer tissue differentiation, with results available within seconds of cauterization [61].

A multicenter study evaluating REIMS for breast cancer across sites in the United Kingdom, Europe, and Canada demonstrated the feasibility of creating and using global classification models, achieving 97.1% and 98.6% correct classification for leave-one-site-out and leave-one-patient-out cross validation, respectively [62]. In soft tissue sarcoma, REIMS achieves 95.5% overall diagnostic accuracy with 96.6% specificity for leiomyosarcoma detection [69]. A comprehensive systematic review of REIMS applications across multiple surgical specialties demonstrates its emerging role in real-time intraoperative tissue identification with promising results for accuracy, sensitivity, and specificity across eight surgical specialties [70]. Foundation models specifically designed for REIMS data demonstrate state-of-the-art performance with 82.4% AUC in tissue classification [71]. A 2025 study investigating REIMS for real-time overall survival time classification of glioblastoma samples demonstrated the feasibility of integrating REIMS into intraoperative diagnostics, offering real-time insights that can guide personalized treatment strategies [72].

Alternative Mass Spectrometry Platforms

Desorption Electrospray Ionization Mass Spectrometry Imaging (DESI-MSI) provides molecular mapping capabilities with 98.6% agreement with histopathology in

pancreatic cancer margin assessment [63]. The MasSpec Pen represents breakthrough handheld technology achieving 91.5% overall agreement with pathological diagnosis, with 95.5% sensitivity and 89.7% specificity in breast cancer cases [73]. The MasSpec Pen demonstrated 93.8% overall agreement with final postoperative pathology reports during pancreatic surgeries, with analysis completed in approximately 15 seconds per sample [64]. A recent study validated the MasSpec Pen in breast cancer, achieving 96.3% accuracy with sensitivity and specificity both exceeding 96% [65].

Recent developments include untargeted swab touch spray-mass spectrometry analysis demonstrating feasibility for intraoperative breast margin assessment, achieving 90.9% sensitivity and 98.8% specificity in the validation set [66]. The entire workflow, from swab TS-MS analysis to margin prediction, can be completed within 5 minutes with high accuracy, demonstrating the feasibility of this approach to assist intraoperative decision-making [66].

Immunotherapy Integration in Surgical Oncology

Perioperative Checkpoint Inhibitor Therapy

Perioperative immunotherapy demonstrates significant clinical promise for preventing metastatic progression and enhancing immune surveillance. A comprehensive 2024 meta-analysis of 8 randomized clinical trials including 3,387 patients with resectable NSCLC confirmed that neoadjuvant immunotherapy plus chemotherapy reduced the risk of recurrence or death by 43% (HR 0.57; 95% CI, 0.50–0.66; $P < 0.001$) and increased the pathological complete response (pCR) rate by over 5-fold (RR 5.58; 95% CI, 4.27–7.29) compared to chemotherapy alone [74]. This association was not significantly modified by patient characteristics or tumor- or treatment-related factors, including high or low tumor *PD-L1* status [74].

The FDA approved perioperative durvalumab with platinum-containing chemotherapy for resectable non-small cell lung cancer (NSCLC) in August 2024, based on the AEGEAN trial demonstrating significantly greater event-free survival (EFS) (HR 0.68; 95% CI, 0.53 to 0.88) and pCR (17.2% vs. 4.3%) [21, 75]. The CheckMate-77T trial led to FDA approval of perioperative nivolumab in October 2024, demonstrating significantly longer EFS (HR 0.58) and a higher pCR rate (25.3% vs. 4.7%) in resectable NSCLC patients [22, 76]. Patients with stage III N2 disease had improved EFS with nivolumab versus placebo (HR 0.46; 1-year EFS 70% vs. 45%) and higher pCR (22.0% vs. 5.6%) [76]. The KEYNOTE-671 trial, supporting FDA approval of perioperative pembrolizumab for resectable NSCLC in October 2023, demonstrated statistically significant improvements in both EFS and overall survival [23, 77].

A meta-analysis of phase 2/3 trials in resectable gastric or gastroesophageal junction cancer demonstrated that perioperative chemoimmunotherapy achieved nearly threefold increase in pCR rate (risk ratio 2.80; 95% CI, 1.68–4.67), with a 24% relative reduction in progression or death (EFS HR 0.76) and 22% reduction in mortality (OS HR 0.78) [78, 79]. Table 4 summarizes the clinical efficacy and patient selection criteria.

Table 3. Advanced Surgical Technologies – Comprehensive Analysis

Technology	Cancer types	Diagnostic performance	Key clinical benefits	Key evidence	References
Robotic-assisted surgery	Colorectal, prostate, gynecologic, pancreatic	Not applicable (technical platform)	3-year locoregional recurrence 1.5% vs 4.0%; reduced blood loss, LOS, and conversion; up to 43% less tissue damage with force feedback	REAL Trial; da Vinci 5 thoracic and colorectal series	42,43,44–47,50
Fluorescence-guided surgery (ICG)	Gastric, hepatocellular, head and neck, liver	Tumor delineation ≥95%	5-year OS 80.6% vs 66.7% (P=0.018); HR 0.61 for all-cause death; higher R0 rates and lower early recurrence	FUGES-012 RCT; hepatobiliary and head–neck cohorts	11,55,57,58,60
REIMS (intraoperative MS)	Breast, soft tissue sarcoma, oral cavity, brain	Sensitivity 93.4%; specificity 94.9%; global model accuracy up to 97.1%	Real-time tissue classification from electrosurgical smoke; feasible cross-site global models	Systematic review; multicenter breast and sarcoma series	12,61,62,69–72
DESI-MSI imaging	Pancreatic, breast, brain	Agreement with histopathology up to 98.6%	High-resolution molecular margin mapping; supports intraoperative decision-making	Pancreatic and CNS validation cohorts	63,67
MasSpec Pen	Breast, pancreatic, ovarian	Accuracy up to 96.3% in breast; sensitivity and specificity >96%	Non-destructive, label-free analysis; ≈15-second turnaround per sample; high concordance with final pathology	Pancreatic and breast intraoperative trials	64,65,73
Swab touch spray-MS	Breast cancer margins	Sensitivity 90.9%; specificity 98.8%	Complete workflow (sampling–analysis–prediction) within ≈5 minutes; accurate margin assessment	Prospective validation study in breast surgery	66

Abbreviations: ICG, indocyanine green; OS, overall survival; HR, hazard ratio; LOS, length of stay; R0, microscopically margin-negative resection; REIMS, rapid evaporative ionization mass spectrometry; MS, mass spectrometry; DESI-MSI, desorption electrospray ionization mass spectrometry imaging; CNS, central nervous system.

Table 4. Therapeutic Technologies and Clinical Applications

Therapeutic approach	Mechanism of action	Key clinical efficacy outcomes	Regulatory status	Safety profile	References
Perioperative durvalumab (resectable NSCLC)	*PD-L1* blockade	EFS HR 0.68; pCR 17.2% vs 4.3% vs chemotherapy alone	FDA approved (August 2024)	Grade 3–4 AEs in 42.4% of patients; manageable toxicity	21,75
Neoadjuvant ICI + chemotherapy (NSCLC)	Immune checkpoint inhibition plus cytotoxic chemotherapy	43% reduction in recurrence or death (EFS HR 0.57); pCR RR 5.58 vs chemotherapy	Meta-analysis of phase III RCTs; emerging standard of care	Consistent benefit across PD-L1 and clinical subgroups	74
Perioperative nivolumab (resectable NSCLC)	*PD-1* blockade	EFS HR 0.58; pCR 25.3% vs 4.7%; improved 1-year EFS in stage III N2	FDA approved (October 2024)	Safety comparable to chemotherapy	22,76
Perioperative pembrolizumab (resectable NSCLC)	*PD-1* blockade	Statistically significant OS and EFS improvements vs chemotherapy	FDA approved (October 2023)	Acceptable and manageable safety profile	23,77
Perioperative chemo-immunotherapy (gastric / GEJ)	Combination of ICIs with perioperative chemotherapy	Nearly 3-fold increase in pCR (RR 2.80); EFS HR 0.76; OS HR 0.78	Phase II–III clinical trial data; under regulatory evaluation	Enhanced but acceptable toxicity; benefit–risk favorable	78,79
ELI-002 2P KRAS vaccine	Lymph node–targeted mutant KRAS peptides	KRAS-specific T-cell response in ≈84% of patients; mRFS 16.33 months; mOS 28.94 months; 77% risk reduction with strong T-cell responses	Phase I/II trials in pancreatic and colorectal cancer	Well tolerated; no unexpected safety signals	80,81
ELI-002 7P KRAS vaccine	Off-the-shelf mutant KRAS peptides (7 variants)	KRAS-specific T-cell responses in 99% of evaluable patients; 145.3-fold mean increase	Phase I/II AMPLIFY-7P trial	Well tolerated	82,83
Nanoparticle-based drug delivery	Enhanced permeability and retention; targeted cytotoxic delivery	40–60% reduction in systemic toxicity (e.g., cardiotoxicity) with preserved anticancer efficacy	Multiple FDA-approved nanoformulations across tumor types	Improved tolerability vs conventional formulations	13,84,85,88–90

Abbreviations: NSCLC, non-small cell lung cancer; *PD-L1*, programmed death-ligand 1; *PD-1*, programmed cell death protein 1; EFS, event-free survival; OS, overall survival; pCR, pathological complete response; AE, adverse event; ICI, immune checkpoint inhibitor; GEJ, gastroesophageal junction; RCT, randomized controlled trial; mRFS, median relapse-free survival; mOS, median overall survival; FDA, Food and Drug Administration.

Novel Immunomodulatory Approaches

Innovative approaches include personalized cancer vaccines utilizing patient-specific tumor-derived antigens demonstrating significant efficacy in preventing recurrence. The ELI-002 2P vaccine targeting KRAS mutations in pancreatic and colorectal cancer showed that at an extended median follow-up of 19.7 months, approximately 84% of evaluable patients generated mutant KRAS-specific T-cell responses, with median relapse-free survival of 16.33 months and median overall survival of 28.94 months [80, 81]. Clinical efficacy correlated with the magnitude of T cell responses specific to mutant KRAS induced by ELI-002, with a 77% reduction in the risk of relapse or death in patients with strong T-cell responses [81].

The ELI-002 7P expanded spectrum vaccine covering seven KRAS mutations induced mutant KRAS-specific T cell responses in 99% of evaluable patients (89/90), with an average increase of 145.3-fold over baseline responses and a median fold increase of 44.3-fold [82, 83]. The ELI-002 7P formulation is designed to provide immune response coverage against seven of the most common KRAS mutations present in 25% of all solid tumors [83].

A landmark observational study published in Nature in 2025 found that patients with cancer who received mRNA-based COVID vaccines within 100 days of starting immune checkpoint therapy were more than twice as likely to be alive after three years compared to those who did not receive the vaccine [86]. The vaccinated group had a 3-year overall survival rate of 55.7% compared with 30.8% in the unvaccinated group, translating to a 49% reduction in cancer-associated mortality risk [86]. The study demonstrated that COVID-19 mRNA vaccines act as immune modulators capable of sensitizing tumors to immune checkpoint inhibitors, with patients receiving the vaccine within 100 days of ICI initiation achieving near doubling of median survival from 20.6 months to 37.3 months in advanced lung cancer [86, 87].

Nanotechnology and Targeted Drug Delivery
Advanced Drug Delivery Systems

Nanotechnology-based drug delivery systems revolutionize cancer therapy through enhanced biodistribution profiles and reduced systemic toxicity. Nanoparticles have the ability to encapsulate drugs and transport them directly to tumor cells, ensuring higher concentration of therapeutic agents at the targeted site while significantly reducing systemic toxicity commonly associated with conventional chemotherapy [13, 84]. Recent advances focus on tumor microenvironment-responsive intelligent delivery systems, with clinical studies demonstrating 40–60% reduction in cardiotoxicity compared to conventional formulations while maintaining therapeutic efficacy [13, 84].

Specific clinical data highlights the safety advantages of nanomedicines. Liposomal doxorubicin formulations have been shown to reduce the incidence of heart failure significantly compared to conventional anthracyclines (6% vs. 21%, P = 0.0002), allowing for safer long-term administration [85, 88]. Comparative analysis of multi-drug cancer nanomedicine demonstrated that combination nanotherapy results in the best overall survival rates, with 56% of studies demonstrating complete or partial survival benefits [89]. The mechanisms for reduced cardiotoxicity are attributed to lower heart accumulation while maintaining anti-tumor efficacy, with liposomal formulations showing lower maximum plasma concentrations in the myocardium [90].

Theranostic Applications

Theranostic nanoparticles provide integrated diagnostic and therapeutic capabilities within single platforms, enabling personalized treatment approaches and real-time therapy monitoring. Nanoparticles can be loaded with chemotherapeutic agents while being functionalized with contrast agents for imaging, enabling clinicians to track drug distribution and efficacy in real-time [91]. Lipid-core-shell nanoparticle platforms have been shown to co-deliver chemotherapy regimens along with siRNA targeting PD-L1, enabling combined chemotherapy and immunotherapy approaches [92].

Targeted delivery systems represent a major advancement in nanotechnology-based cancer therapy, offering the potential for highly specific and effective treatment with minimized side effects. Functionalization of nanoparticles with ligands like peptides, antibodies, aptamers, or small molecules enables precise targeting of cancer cell surface receptors, which are often overexpressed in tumor cells compared to normal cells [93]. For example, the 4WJ-EGFRapt-miR-375-PTX system leverages EGFR-mediated targeting to co-deliver miR-375 and paclitaxel, effectively inhibiting tumor proliferation, migration, and invasion [94].

Implementation Challenges and Future Directions
Healthcare System Integration

Successful implementation of advanced surgical technologies requires comprehensive healthcare system adaptation. Key barriers include high capital investment requirements, specialized training needs, workflow integration challenges, and reimbursement uncertainties [95]. Strategies for overcoming these barriers include phased implementation approaches, collaborative training programs, standardized outcome metrics, and evidence-based reimbursement frameworks [96-99].

Regulatory Considerations

Regulatory frameworks for AI-based surgical technologies continue to evolve, with the FDA and EMA developing specific guidance for machine learning-based medical devices [97, 100, 101]. Key considerations include algorithm validation requirements, continuous learning system monitoring, and cybersecurity standards. The FDA approval of the Shield blood test for colorectal cancer screening and multiple perioperative immunotherapy regimens demonstrate successful pathways for novel technology approval [24, 21–23, 102-105].

Future Research Priorities

Priority research areas should focus on addressing key gaps in current evidence, including expanding biomarker

profiling beyond *PD-L1* and MSI to incorporate additional predictive markers such as tumor mutational burden, tumor-infiltrating lymphocyte density, and circulating tumor DNA for minimal residual disease detection [78, 106]. Prospective trials must move beyond accuracy and efficiency to relational endpoints such as trust, comprehension, and satisfaction [98, 107]. Integration of multiple technologies including AI, robotics, fluorescence imaging, and mass spectrometry into unified surgical platforms represents the future of precision cancer surgery [99, 108].

In conclusions, the convergence of precision medicine, AI, robotics, advanced imaging, and molecular technologies is fundamentally transforming cancer surgery toward personalized, data-driven interventions with measurable clinical improvements. Precision medicine approaches utilizing genomic profiling and circulating tumor DNA achieve high sensitivity and specificity in cancer detection and recurrence prediction. AI systems demonstrate remarkable accuracy in outcome prediction and surgical guidance, while robotic platforms provide significant advantages in challenging scenarios with reduced tissue damage. Fluorescence-guided surgery and mass spectrometry-based techniques enable real-time intraoperative tissue characterization with diagnostic accuracy exceeding 95%. Perioperative immunotherapy integration demonstrates substantial reductions in recurrence risk and improvements in pathological complete response rates. Novel immunomodulatory approaches, including targeted vaccines and mRNA-based immune stimulation, show promising results for preventing recurrence. Implementation challenges including costs, standardization requirements, and training needs must be systematically addressed for widespread adoption. Future research should focus on integrating multiple technologies into unified platforms, developing comprehensive biomarker panels for patient selection, and conducting prospective trials with standardized endpoints. The continued evolution of these technologies promises to further improve cancer surgery outcomes and patient survival.

Author Contribution Statement

Alireza Negahi, Mehdi Khosravi-Mashizi, and Hossein Najdsepas conceived and designed the study and acquired the data. Seyede Arefe Mousavi-Beni, Reza Shahrokhi, and Amirhosein Naseri contributed to data analysis and interpretation. Fatemeh Jayervand, Amirhossein Shahbazi, and Amirhossein Rahmani performed data analysis and drafted the manuscript. Hossein Negahban and Hossein Neamatzadeh critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Ethics Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of Data and Materials

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare no conflicts of interest.

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