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Factors of Organizing Surgical Treatment of Upper Gastrointestinal Cancers and Patient Survival: Real-World Data

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Aim: to analyze the safety and effectiveness of the method of cold snaring resection with preliminary hydropreparation when removing superficially colorectal epithelial neoplasms with a diameter of 5 to 25 mm.

Material and methods. The number of complications and disease recurrence after endoscopic excisions by “cold” snaring resection with preliminary hydropreparation of superficially neoplasms with a diameter of 5 to 25 mm was assessed.

Results. Neoplasms were removed in a single block in 89/122 (72.95 %) cases. Neoplasms with a diameter of 5 to 9 mm were excisions in a single block in 100 % of cases, with a diameter of 9 to 14 mm in 28/30 (93.33 %) cases, with a diameter of 15 to 19 mm in 12/38 (31.57 %) cases. According to the results of a lifetime pathoanatomic examination of the removed material, serrated dysplasia (serrated dysplasia, low grade) was detected in 76 cases; micro vesicular hyperplastic polyps (Hyperplastic polyp, micro vesicular type MVHP) were established in 9 cases; hyperplastic polyps containing goblet cells (Hyperplastic polyp, goblet cell GCHP) were in 5 cases; tubular adenoma with dysplasia (Tubular adenoma, low grade) was in 32 cases. Delayed bleeding and perforation of the intestinal wall, both at the time of resection, and in the delayed period was not observed. No local recurrence was detected in the groups of patients with neoplasms diameters of 5–9 and 10–14 mm. One case of local recurrence was detected in a group of patients with a neoplasms diameter from 15 to 19 mm (1/38 = 2.63 %) and one case in a group with a neoplasms diameter of 20–25 mm (1/5 = 20 %).

Conclusions. Cold endoscopic snaring resection of colorectal epithelial neoplasms with preliminary hydropreparation in the submucosa is a safe and effective method of excisions superficially epithelial neoplasms of the colon with a diameter of 5 to 19 mm.

Key words: colorectal epithelial neoplasm, cold snaring mucosal resection, serrated dysplasia

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Факторы организации хирургического лечения опухолей верхних отделов гастроинтестинального тракта и выживаемость пациентов: данные клинической практики

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Цель исследования: оценить влияние факторов организации эзофагэктомии и гастрэктомии на прогноз у пациентов в реальной онкологической практике.

Основное содержание. Изучены некоторые факторы организации и оценки хирургического лечения опухолей верхних отделов гастроинтестинального тракта, активно обсуждаемые в индексируемых в PubMed оригинальных статьях. Анализировали итоговые результаты первичных оригинальных зарубежных исследований. Метаанализы и систематические обзоры в анализ не включали. Поиск научных публикаций проводили

с использованием PubMed и Google по следующим ключевым словам: «esophageal cancer», «gastric cancer», «surgical factors», «survival», «prognosis», etc. Временной горизонт поиска охватывал период с 2017 по 2021 г. При необходимости в исследование включали статьи за другие годы. Источники отбирали вручную, фильтры не применяли. Оперативное лечение рака пищевода и желудка является одним из наиболее технически сложных вмешательств, что отражается на клинических исходах у пациентов. Минимально инвазивные методы (лапароскопия и торакоскопия) становятся частью стандартной практики и должны внедряться после структурированного и контролируемого обучения хирургической бригады. Активно изучается практическая применимость новых хирургических технологий на основе роботизированных устройств. Вопросы оптимального планирования работы операционных бригад и определения других факторов, влияющих на результативность и безопасность хирургического лечения, остаются предметом дискуссий хирургов, онкологов, организаторов здравоохранения.

Выводы. Дополнительный мониторинг реальной онкологической практики позволит определить роль множества новых модифицируемых факторов организации онкохирургического лечения. Анализ этих факторов приведет к усовершенствованию действенных стратегий увеличения продолжительности и повышения качества жизни пациентов после эзофагэктомии и гастрэктомии.

Ключевые слова: организация здравоохранения, общественное здоровье, показатели качества, рак пищевода, рак желудка, хирургия

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Introduction

Surgical resection is an essential attribute of the radical treatment of cancer of the esophagus and stomach. The significant risk of recurrence and the low 5-year survival of patients after surgical removal of tumors of the upper gastrointestinal tract suggest the need for further identification of modifiable clinical factors that affect long-term outcomes.

In a number of relevant and authoritative foreign clinical studies, the influence of the weekend factor and the effect of choosing individual days of the week for surgery on the prognosis and survival in common types of malignant tumors (tumors of the esophagus, abdominal neoplasms, oncogenic diseases, etc.) is discussed [1–5]. For example, the Swedish National Oncology Quality Study suggests that the accuracy and accuracy of surgical technique deteriorates towards the end of the working week. Findings suggesting a lower overall 5-year survival after esophagectomy performed Wednesday-Friday compared to Monday-Tuesday [6].

The effect of weekend hospitalization was reflected in 30-day mortality among patients with gastrointestinal tumors observed in clinics in England and Wales [7, 8]. Similar results on the influence of the choice of the day of the week for elective surgery on the prognosis and development of complications in gastric cancer in China were published by oncologists in 2017 [9].

In contrast, a large population-based cohort study, organized in the Netherlands, did not support the assumption of an association of individual

days of the week with survival in patients with esophageal cancer with a potentially curable clinical profile treated in the national oncology network [10]. Also, there was no statistically significant association between days of the week and outcomes in patients after D2 gastrectomy in Germany [11].

Heated discussions of oncologists and healthcare organizers on the issues of optimal planning of the work of surgical teams and the identification of other primary causal factors that affect the effectiveness and safety of surgical treatment of malignant neoplasms do not cease abroad [2, 12–14]. However, there are not enough reports on this topic in the domestic scientific literature.

The aim of the study — to determine the influence of some factors in the organization of esophagectomy and gastrectomy on the prognosis in patients in real oncological practice abroad.

Some factors of organizing and evaluating the surgical treatment of tumors of the upper gastrointestinal tract, actively discussed in original scientific articles indexed in PubMed for 2020–2021, were studied. In this scientific work, the final results of primary original foreign studies were analyzed. Meta-analyses and systematic reviews were not included in the analysis.

Scientific publications were searched using PubMed and the Google system for the following keywords: «esophageal cancer», «gastric cancer», «surgical factors», «survival», «prognosis», etc. The search time horizon covered the period from 2017 to 2021. Sources were selected manually, filters were not applied.

Cancer of the esophagus and stomach are combined into one group due to the general features of treatment and patient care [15]. The use of an endoscope for mucosal resection or submucosal dissection is the preferred surgical technique for early and superficial (exophytic growth) cancer of the esophagus and stomach (T — *in situ*, T1a without multifocal lesions) [16]. Surgical resection is performed for early-stage cancer that is not suitable for endoscopic resection and may be performed to cure [17].

The role of the surgeon, in this case, is to implement the following medical processes: 1) the choice of an appropriate surgical technique by assessing the extent of the tumor, including on the basis of the results of laparoscopy; 2) determining the degree of readiness of the patient in the framework of the implementation of an interdisciplinary approach; 3) performing a surgical operation; 4) taking responsibility for organizing comprehensive medical care in the perioperative period [17].

Despite the general patterns, the algorithms for the organization of surgical treatment, which determine the success of esophagectomy and gastrectomy, have some peculiarities.

Esophagectomy

Surgery is part of the definitive treatment of patients with esophageal cancer in about 25 % of cases [18]. Surgical treatment of esophageal cancer is one of the most technically complex interventions, which naturally affects the clinical outcomes of patients. The immediate and long-term results of treatment after esophagectomy directly depend on many factors. First of all, this is the stage of the disease at the time of surgery (according to the cumulative data, the overall 5-year survival rate after radical treatment rarely exceeds 43 % [19], up to 70 %, about 30 % and not more than 10 % at 0–I, II, III–IV stages, respectively [6]), the morphological structure of the tumor, the presence and severity of concomitant pathology, and much more. It is important to evaluate the impact of a complex of potentially modifiable elements of the organization of oncosurgical care in various healthcare systems on outcomes in patients after esophagectomy.

The choice of method of technical manipulation on the esophagus may affect the outcomes of treatment in patients. Today, minimally invasive methods (laparoscopy and thoracoscopy [20]) become part of standard practice and should be implemented after structured and supervised training of the surgical team [17]. The practical applicability of new surgical technologies based on robotic devices for manipulations in the upper

gastrointestinal tract is being actively studied [21, 22].

Among the latest developments, we should also mention fluorescent laparoscopy, which allows for intraoperative assessment of blood flow. For example, in Germany, since December 2020, the practical use of the Visionsense laparoscope has begun as a standard of care for Ivor-Lewis esophagectomy. Livsmed devices are considered promising (especially for clinics that do not have access to robotics), providing robotic triangulation. The advantages of triangulation are especially evident in lymphadenectomy in anatomically difficult to reach areas and in reconstructions (eg, esophago-gastroanastomosis, esophagojejunostomy).

It must be emphasized that the definitive and reliable benefits of new surgical techniques in terms of survival among patients with esophageal cancer, as well as to establish their clinical and economic characteristics in everyday practice, have yet to be determined. An important role in organizing high-quality work with complex laparoscopic instruments is played by the qualifications and accreditation of specialists [22]. The professional experience of the surgeon is of great importance [23], well-coordinated work of a team of doctors and other healthcare professionals, organization of work processes to ensure the provision of quality medical care.

With the introduction of new surgical techniques, medical organizations are increasingly required to modernize their quality control systems, including updating the so-called criteria and digital standards. In foreign literature (J.Hoepfner et al. (2021) [20]) established innovative quality assessment criteria (indicators) for the diagnosis and surgical treatment of esophageal cancer, allowing the development of effective measures to improve current oncological practice (Table) [20].

Standard surgical treatment for esophageal cancer usually takes several hours to complete. For example, in Sweden, the average duration of an esophagectomy is about 6.5 hours [6].

Can a heavy workload affect the concentration and degree of professional “burnout” of surgeons?

This research question was previously explored in a large population-based cohort study performed in Sweden (J. Lagergren et al., 2016 [6]). Almost all cancer patients ($n = 1799$) after esophagectomy performed between January 1, 1987 and December 31, 2010 and followed up to November 13, 2014 were analyzed. It should be noted that the study was made possible due to the coherence and organization of high-quality work of administrative databases of medical records, specialized national clinical and demographic registers: the Swedish

Table. Indicators of the quality of diagnosis and surgical treatment of esophageal cancer, developed based on the principles of evidence-based medicine (modified and adapted from: J. Hoepfner et al. (2021) [20], Creative Commons Attribution 4.0 International License)

| Indicator | Literature | Level of Evidence | Category |
|--|----------------------|-------------------|-----------|
| Minimum number: ≥ 20 resections/year/clinic | [24–27] | 3 | Structure |
| Using chromoendoscopy to detect intraepithelial neoplasia | [28] | 1b | Process |
| Use of deep biopsy methods such as: “deep biopsy”, “bite-on-bite biopsy” | [29, 30] | 2a | |
| Combined EUS examination (possibly with fine needle biopsy) to detect locoregional lymph node metastases | [31, 32] | 1b | |
| Use of PET-CT to identify affected lymph nodes or distant metastases | [33–36] | 2a | |
| Preoperative assessment: – cardiovascular, pulmonary, hepatic and metabolic functions, – compliance (geriatric practice), – nutritional status (BMI, nutritional risk assessment, mini nutritional assessment) | [37–43] | 2b | |
| The use of pre-rehabilitation and accelerated rehabilitation technologies after surgery to improve convalescence | [44–47] | 1b | |
| Perform endoscopic mucosal resection or endoscopic submucosal dissection for: – submucosal infiltration <500 μm , – absence of lymphovascular infiltration (L1, V1), – degrees of tumor tissue differentiation $<G3$, – low risk tumors (T1m1-2, T1sm1 “low risk”) | [37], [48–53] | 2a | |
| Performing primary esophagectomy for: – high risk (sub)mucosal tumors (T1a, T1sm1), – submucosal tumors (T1sm2–3), – T2N0 tumors | [54] | 3 | |
| Application of the concept of multimodal therapy in T2N+ and T3N0/N+ tumors: – neoadjuvant chemoradiotherapy, – perioperative chemotherapy → and surgical resection | [52–55] | 1b | |
| Use of minimally invasive surgical technique to reduce the severity of complications: – hybrid technology, – completely minimally invasive technique | [56], [57] | 1b | |
| Performing definitive/radical chemoradiotherapy for unresectable tumors or functionally inoperable patients (with the possibility of performing a “rescue resection”) | [58–60] | 2a | |
| – Optimization of intraoperative airway management – Epidural anesthesia | [61, 62] | 3 | |
| Structured assessment of complications according to the Esophagectomy Complications Consensus Group | [63, 64] | 2b | |
| Reduction of negative indicators: – mortality, – number of anastomotic leaks/postoperative complications = by treatment in specialized centers | [24–26], [65, 66] | 3 | Outcome |

Cancer Registry, the Swedish Patient Registry, the Swedish Cause of Death Registry.

A comparative analysis of planned esophagectomy performed at the end of the week (Wednesday-Friday) and operations at the beginning of the week (Monday-Tuesday) showed a higher 5-year

mortality from all causes and from the progression of the tumor process when performing operations on the final days of the working week (Hazard Ratio [HR]: 1.13, 95 % CI, 1.01–1.26 and 1.15, 95 % CI, 1.02–1.29, respectively).

When studying the effect for each of the 5 working days, the value of the HR increased from Wednesday to Thursday and then to Friday. Compared with operations on Monday, esophagectomy performed on Friday resulted in an increase in all-cause and disease-related mortality by 46 % and 44 %, respectively (hazard ratio ≤ 1.46 , 95 % CI, 1.15–1.85 and hazard ratio ≤ 1.44 , 95 % CI, 1.13–1.84) [6]. This was the first study to show an association between the days of the week scheduled for surgery and long-term patient survival.

Additional analysis showed no association of working days with 30-day postoperative mortality and reoperation rates [67]. Thus, the found correlation of the working days choice factor with the long-term forecast was not explained by the influence of short-term outcomes. This indicated the presence of other hypothetical factors, for example, fatigue of surgeons, which probably causes a negative impact on the adequacy of the level of tumor dissection in the late postoperative stages. And, accordingly, increasing the risk of local recurrence.

The findings were supported by the results of subsequent studies (included between January 1997 and December 31, 2014) by Lagergren et al., published in 2017, in which the planning of operations for cancer of the esophagus and stomach on the last days of the working week (Thursday or Friday) was associated with an increase in the HR for fatal outcomes. Comparing the outcome of surgery for esophageal and gastric cancer on Friday with surgery on Monday, the adjusted hazard ratio for cancer death was 1.57 (95 % CI, 1.31–1.88). In a separate analysis, for esophageal cancer and gastric cancer, the hazard ratios were 1.45 (0.87–2.39) and 1.70 (1.38–2.09), respectively. The Kaplan–Meier 5-year survival curves also differed depending on the chosen day of surgery [68].

Swedish scientists at the initial stage suggested that the revealed effect was partly due to the excessive level of centralization of oncological care. According to the authors, in the conditions of high-flow centers, surgeons are forced to perform complex, extensive operations (esophagectomy) throughout the entire working week. Thus, it is possible that the attention and accuracy of surgeons' actions decreased by the end of the working week. Another explanation was the lack of medical personnel or the lack of experience of surgeons on duty on weekends. Researchers recommend considering scheduling extensive surgeries for the start of the workweek [6].

Interestingly, J. Lagergren et al. (2017) found effects of working day selection on long-term

prognosis in cohorts of patients with other gastrointestinal tumors, but did not find them for a number of common tumors (breast cancer, prostate cancer, etc. [68]). Because of these observations, clinicians are debating the need to review the evidence base to develop or update recommendations for scheduling surgical teams in cancer centers. J. Lagergren et al. did not reach an unequivocal and convincing conclusion about the causes of the observed phenomena, although they believe that the patterns found can be extended to other countries with a Swedish-style model for organizing cancer care.

A similar study by E. Visser et al. (2017) (covering 2005–2013) in the Dutch health care system found no association between days of the workweek and long-term outcomes in patients after esophagectomy [10].

E. Visser et al. emphasize that the results obtained in the J. Lagergren et al. studies are unlikely to be explained by over-centralization of cancer care. Measures for centralization [69] and an increase in the flow of patients lead to good, positive results (in the Netherlands, at least 20 esophagectomy are performed in each centralized clinic per year): high professionalism and extensive experience of all medical specialists, proven specialization and certification in gastrointestinal surgery, adaptation of surgeons to increased workloads and complex work regimes [10]. In addition, it is likely that short-term outcomes in patients better reflect the skill of surgeons and the quality of surgical treatment, and they did not depend on the planned day of surgery in the studies cited.

With the development of medical technologies in routine clinical practice, there is a natural transition to the use of minimally invasive surgical approaches. Randomized controlled trials (RCTs) and meta-analysis suggest that minimally invasive esophagectomy is likely associated with better long-term survival, although more evidence needs to be obtained from studies with larger patient cohorts [12].

In the Dutch population study D.M. Voeten et al. (2021) [70] the question was again raised about the association of the factor of choosing the day of elective surgery with the results of surgical treatment, but on the basis of a minimally invasive technique. We analyzed 4102 cases of minimally invasive interventions for tumors of the upper gastrointestinal tract (2968 patients with esophageal cancer and 1134 patients with gastric cancer). The minimally invasive technique is the standard of care in the Netherlands. The use of such a technique in the era of centralization (short-term outcomes: 30-day mortality, 30-day readmission rate, length of stay in the intensive

care unit, complication rate, composite quality assessment criterion — “textbook outcome”, etc.) has not been associated with the choice of the day of the operation. A definite advantage of the D.M. Voeten et al. study design [70] began to take into account the factor of variability in the frequency of operations on the days of the week between clinics.

Gastrectomy

At the present stage, significant progress has been made in the early diagnosis of gastric carcinomas, due to the improvement of the methodological approach and the updating of endoscopic equipment. However, the results of treatment of malignant neoplasms of the stomach remain unsatisfactory. Medical researchers around the world are searching for potentially modifiable factors that affect prognosis with the ultimate goal of improving the life expectancy of patients with gastric cancer [71]. For example, in a recent study by Y. Li et al. (2022) [72], it is emphasized that a combination of factors such as the stage of the disease according to the TNM system at the time of diagnosis, the number of cycles of chemotherapy are closely associated with the risk of postoperative recurrence during the follow-up period for gastric cancer over 3 years.

A wide range of studies have examined a variety of factors that determine mortality rates and the development of complications in patient populations after gastrectomy [73–77]. It has been shown that minimally invasive laparoscopic interventions are beneficial in terms of short-term outcomes and long-term survival as an alternative to the “open technique” in certain circumstances in the surgical treatment of patients with gastric cancer [78]. However, a significant proportion of researchers believe that additional research is needed to finally establish all the possible advantages or disadvantages of innovative surgical approaches compared to common classical techniques [79, 80].

Some factors of planning the work of the operating team with a possible impact on the prognosis in patients have been identified. Chinese clinicians (Li et al 2017) found a hypothetical effect of planning the day of the week (for surgery) on the development of postoperative complications and long-term survival [9]. It was found that patients who underwent gastrectomy on the last weekdays of the week (Wednesday–Friday) are more at risk of developing postoperative complications. The choice of a day from the chain of days of the working week for the operation was one of the independent indicators of the prognosis in cancer

patients after surgical treatment of gastric cancer (Figure). However, in the group of patients with complications, the effect of choosing the day of surgery was statistically significantly weaker.

Surgical treatment of gastric cancer in the early stages (I–II) in Chinese patients led to a lower incidence of complications, relapses and a better prognosis if it was planned at the beginning of the working week in conditions of good patient preparedness. Thus, according to Chinese researchers, proper planning of the operating room and high-quality perioperative management of the patient can help reduce the proportion of postoperative complications and improve prognosis.

The observations of Chinese specialists were not confirmed in the observational study by F. Berlth et al. (2018) [11] (analyzed data for the period from June 1996 to April 2016), carried out on the basis of data from surgical treatment of gastric adenocarcinoma (total resection or subtotal resection with D2-lymphadenectomy) at the University Hospital of Cologne. A total of 460 patients were included in the analysis, 71 % men and 29 % women. The average age was 65 years. The distribution by day of the week was the same and ranged from 86 cases (Wednesday) to 96 cases (Tuesday).

Survival analyzes between relatively clinically homogeneous samples of patients did not reveal any association of days of the week (Mon/Tue versus Wed/Thu/Fri) with outcome measures ($p = 0.863$; $p = 0.30$, respectively). Treatment outcomes did not differ in terms of mortality during the first 90 days after surgery ($p = 0.948$).

Thus, the German study, although performed on the basis of data from one center, did not prove the presence of a statistically significant effect of the factor of planning the day of the week for performing gastrectomy on treatment outcomes in patients with gastric adenocarcinoma. This study also demonstrated that hypothetical factors such as variability in the experience of the operating team and the quality of the surgical technique practiced on different days of the week, including weekends, may not be reflected in patient outcomes after gastrectomy performed at the University of Cologne.

However, given the limitations of this single-centre analysis, F. Berlth et al. argued in favor of conducting larger cohort studies in the German healthcare system to confirm findings before making final adjustments to clinical guidelines [11].

Conclusion

In general, the current data of the scientific literature indicate the critical importance of the qualifications of the operating team in the chain of factors that determine the immediate prognosis

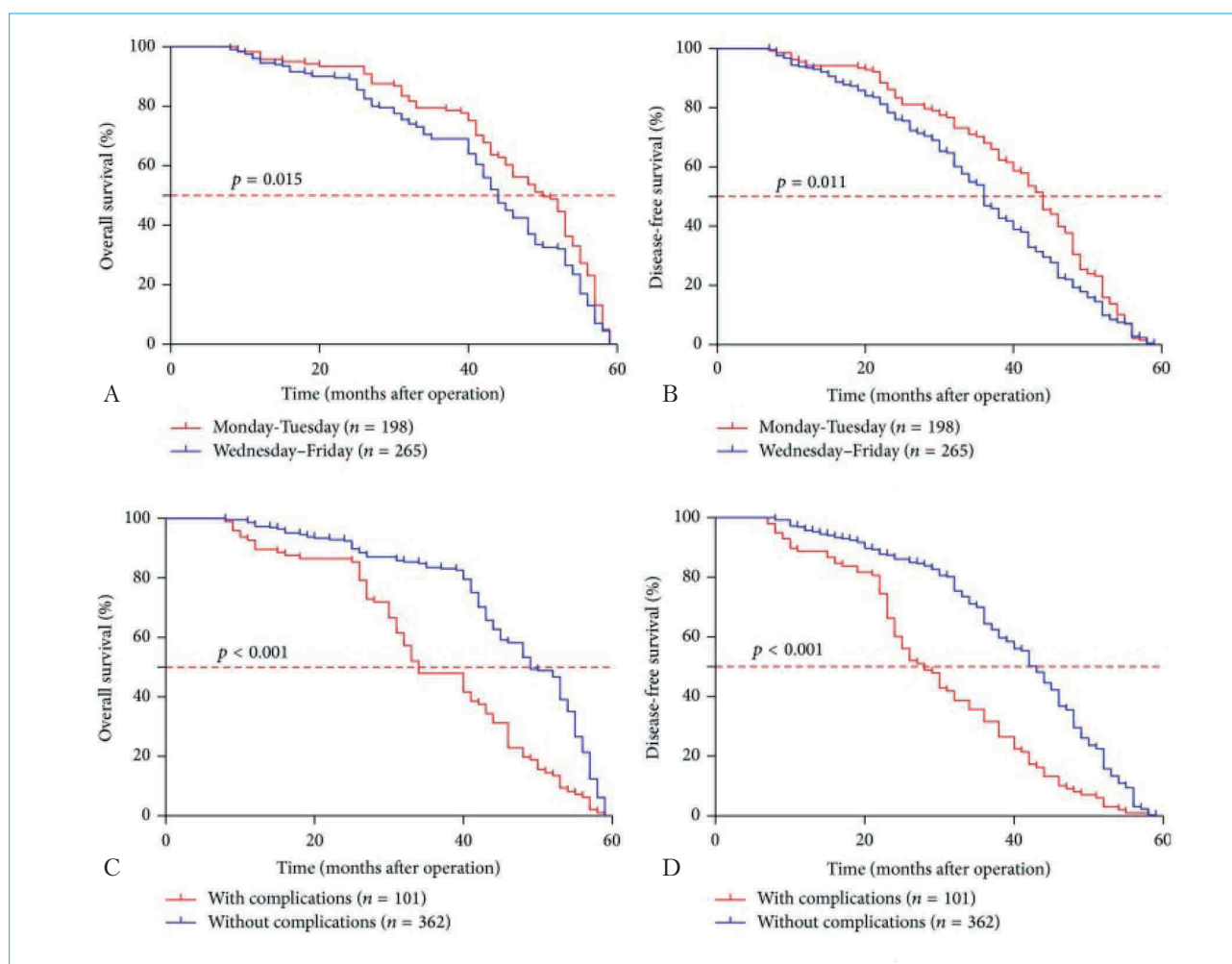


Fig. Influence of the factor of choosing the day of the week for elective gastrectomy and the factor of development of postoperative complications on the overall life expectancy and disease-free survival. Five-year overall survival and disease-free survival were statistically significantly lower in patients operated on Wednesday-Friday compared with Monday and Tuesday (A, B). Patients with postoperative complications had significantly lower OS and disease-free survival than patients without complications (C, D) (adapted from: R. Li et al., 2017 [9], Creative Commons Attribution 4.0 International licence)

in patients after esophagectomy and gastrectomy. Randomized clinical trials comparing different surgical approaches also infrequently reveal significant differences in long-term prognosis in patients after surgical treatment of tumors of the upper gastrointestinal tract. Currently, the operation performed by a highly qualified, experienced surgeon improves the chances of curing cancer and reduces the influence of factors caused by the surgical technology used [12]. It is possible that some particular factors directly related to the professional activities of surgeons (workload, qualifications, age and experience, etc.) may seem to have a greater influence on life expectancy in these patients [12].

It should be noted that the publications, as a rule, provide conflicting information about the association between the choice of the day of the

working week for surgical treatment and survival in patients with malignant neoplasms. The discussed results of clinical observations may depend on the national characteristics of the healthcare systems of specific countries, regional ways of organizing high-tech oncological care, the level of its centralization, accreditation of specialists, the availability of certain resources in a medical institution, and a number of other circumstances.

It is necessary to conduct further clinical studies and study data from real oncological practice (for example, administrative databases and specialized cancer registries) to establish the role of the whole set of modifiable factors in the organization of oncosurgical treatment in ensuring long-term survival of patients after esophagectomy and gastrectomy.

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