

**VILNIAUS UNIVERSITETAS**

**MEDICINOS FAKULTETAS**

Baigiamasis darbas

**Skydliaukės vėžio gydymas lazerine abliacija: galimybių tyrimas**  
**Treatment of Thyroid Cancer With Laser Ablation: a Feasibility Study**

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2024-05-07

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## 1. SANTRAUKA

**Darbo tikslas.** Įvertinti lazerinės abliacijos galimybes ir patologinį poveikį pacientams, sergantiems papiline skydliaukės karcinoma.

**Tiriamieji ir metodai.** Pilnamečiai pacientai, kurių skydliaukės mazgas yra iki 4 cm ir kuriems citologiškai įtariama arba patvirtinta skydliaukės karcinoma (V-VI kategorijos Bethesda sistemoje), bei kuriems nustatyta skydliaukės mazgo piktybiškumo požymių echoskopiniame vertinime (III-V kategorijos EU-TIRADS klasifikacijoje) buvo įtraukti į tyrimą. Prieš tiroidektomiją įvertinti skydliaukės mazgai ultragarsu dėl tinkamumo saugiai ir efektyviai lazerinei abliacijai. Atrinktiems pacientams buvo atlikta lazerinė abliacija, po jos – tiroidektomija. Skydliaukės mėginiai su naviku buvo ištirti makroskopiškai naudojant trifenilo tetrazolio chloridą ir histologiškai su hematoksilinu ir eozinu. Skaitmeniniai makroskopiniai vaizdai analizuoti naudojant Fiji (Imagej) programą v.2.15, o histologiniai vaizdai – naudojant HALO AI programą v.3.6.4134. Jei pacientai nebuvo tinkami lazerinei abliacijai, jiems atlikta tiroidektomija, dokumentuojant echoskopinius mazgo išmatavimus. Statistinė analizė atlikta, naudojant R statistinės programinės įrangos paketą V4.3.3, RStudio, IBM SPSS Statistics V.23 ir G\*Power V.3.1.9.4.

**Rezultatai.** Nuo 2023 metų vasario 14 dienos iki 2024 metų balandžio 5 dienos 180 pacientų buvo patikrinti dėl tinkamumo dalyvauti tyrime. Į tyrimą buvo įtraukti 22 pacientai. Lazerinė abliacija buvo galima 8 pacientams, iš kurių 6 pacientai įtraukti į galutinę analizę. Atlikus patologinį skydliaukės naviko ištyrimą, 4 iš 6 pacientų nustatytas mikroskopinis likutinis nepaveikto naviko plotas.

**Išvados.** Lazerinė abliacija yra įmanomas gydymo metodas 17.4% pacientų, sergančių skydliaukės vėžiu, tačiau mikroskopiniai neradikalumo požymiai stebimi iki 66.7%. Turimomis žiniomis tai yra pirmasis tyrimas, kuriame pataloginiais tyrimo metodais įvertintas lazerinės abliacijos metodo radikalumas.

**Raktažodžiai.** Skydliaukės vėžys, papilinė karcinoma, lazerinė abliacija.

## 2. SUMMARY

**Aim.** To evaluate the feasibility and pathological effect of laser ablation in patients with papillary thyroid carcinoma.

**Subjects and methods.** Adult patients with a thyroid node up to 4 cm, cytologically suspected or confirmed thyroid carcinoma (Bethesda V-VI), and evidence of thyroid node malignancy on ultrasound examination (EU-TIRADS III-V) were included. Before thyroidectomy, nodes were evaluated by ultrasound for eligibility for laser ablation. Suitable patients underwent laser ablation followed by thyroidectomy. Specimens with tumors were evaluated macroscopically using triphenyl tetrazolium chloride, and histologically with hematoxylin and eosin. Digital macroscopic images were analyzed using Fiji (Imagej) software v.2.15 and histological images – using HALO AI software

v.3.6.4134. If patients were not suitable for laser ablation, they underwent thyroidectomy, with ultrasound measurements of the node documented. Statistical analysis was performed using R statistical software package V 4.3.3, RStudio, IBM SPSS Statistics V.23, and G\*Power V.3.1.9.4.

**Results.** From 14<sup>th</sup> February 2023 till 5<sup>th</sup> April 2024, 180 patients were screened for eligibility to participate in the study. 22 patients were included in the study. 8 patients were eligible for laser ablation, and 6 were included in the final analysis. Pathological examination revealed a microscopic residual unaffected tumor area in 4 of the 6 patients.

**Conclusions.** Laser ablation is a possible treatment option for 17.4% of patients with thyroid cancer, but microscopic evidence of non-radicality is observed in up to 66.7%. To our knowledge, this is the first study that evaluated the radicality of laser ablation using pathological methods.

**Keywords.** Thyroid cancer, papillary carcinoma, laser ablation.

### 3. PADĖKA

Nuoširdžiai dėkoju savo magistro darbo vadovui prof. Tomui Poškui už kuravimą, mokymą ir konsultacijas tyrimo bei magistro darbo rašymo metu.

Taip pat dėkoju komandai, su kuria kartu vykdėme tyrimą: doc. Augustui Beišai, prof. Virgilijui Beišai, gyd. Anatolij Ostapenko, dr. Donatui Jociui, gyd. Gretai Liubertaitei, gyd. Juliiui Drachneriui, dr. Romenai Laukienei ir matematikui-biostatistikui Eugenijui Jasiūnui.

Padėka įmonei Biolitec (Vokietija), kurie rėmė tyrimą, aprūpino reikalingomis priemonėmis ir lazeriu tyrimui vykdyti.

Padėka Lietuvos Mokslo Tarybai, kurios finansuoto projekto „Skydliaukės židinių pakitimų gydymas lazerine koaguliacija: galimybių tyrimas“ (Reg. Nr. P-ST-22-98, „Studentų tyrimai semestru metu“) lėšomis buvo įsigyti ir tyrime naudoti 2,3,5-trifenil-2H-tetrazolio chlorido dažai.

### 4. ETIKOS KOMITETO LEIDIMAS

Eksperimentiniam prospektyviam tyrimui „Lazerinė abliacija pirminio diferencijuoto skydliaukės vėžio gydyme. Klinikinė studija“ pritarė Vilniaus regioninis bioetikos komitetas (patvirtinimo numeris 2023/2-1481-958). Visi pacientai pasirašė informuotą asmens sutikimo formą. Šis tyrimas buvo atliktas laikantis 1975 metų Helsinkio deklaracijos, peržiūrėtos 1983 metais, etikos normų.

### 5. SANTRUMPOS

EU-TIRADS klasifikacija – Europos skydliaukės vaizdavimo ir duomenų sistemų klasifikacija  
(*angl. European Thyroid Imaging Reporting and Data Systems classification*)

LA – lazerinė abliacija

TA – terminė abliacija

## 6. ĮVADAS

Skydliaukės vėžys yra dažniausiai nustatomas endokrininės sistemos piktybinis susirgimas (1), apie 3 kartus dažniau aptinkamas moterims (2,3). Paskutiniaisiais dešimtmečiais sergamumas šia liga didėja, o daugiausiai sergančiųjų nustatoma aukšto ir vidutinio išsivystymo šalyse (4,5). Tai lemia pagerėjusi skydliaukės ligų diagnostika bei dažnesnis vaizdinių tyrimo metodų taikymas. Ultragarso (UG) tyrimo metu stebint skydliaukės mazgo piktybiškumo požymius (hipoechogeniškumas, mikrokalcinatai, neaiškios, nelygios ribos, intranodulinė kraujotaka, sferinė mazgo forma (aukštis/plotis  $>1$ , *angl. „taller than wide“*), solidinė struktūra (6)) atliekama UG kontroliuojama plonos adatos biopsija ir citologinis aspirato ištyrimas. Tai yra auksinis skydliaukės vėžio diagnostikos standartas (7,8). Apie 40% atvejų citologinis tyrimas nėra pakankamai jautrus nustatyti, ar pacientas serga skydliaukės vėžiu ar ne (9–11). Tiek negalint atmesti piktybinio susirgimo, tiek jį patvirtinus citologinio tyrimo metu, pacientams rekomenduojamas operacinis gydymas. Visi operuojami pacientai rizikuoja patirti galimas bendrąsias operacinio gydymo komplikacijas (kraujavimą, seromos susidarymą) ir skydliaukės chirurgijai specifiskas komplikacijas (laikiną (1-30%) ar nuolatinį (0,5-5%) balso klostės judrumo sutrikimą (12,13) bei laikiną ar nuolatinį kalčio apykaitos sutrikimą dėl pooperacinio hipoparatiroidizmo (iki 3%)) (14). Taip pat pacientams po tiroidektomijos visą likusį gyvenimą reikia vartoti levotiroksino preparatus – sintetinę skydliaukės hormono tiroksino formą (15). Dar daugiau – randas kakle sukelia kosmetines ir psichologines problemas, kurios kartu su fiziologiniais pooperaciniais pokyčiais pablogina pacientų gyvenimo kokybę (16).

Minimaliai invazinės procedūros užima vis svarbesnę vietą modernioje chirurgijoje siekiant sumažinti chirurginio gydymo sukeltus pooperacinius gyvenimo kokybės pokyčius ir personalizuoti gydymą atsižvelgiant į kiekvieno paciento situaciją. Didėjantis terminės abliacijos (TA) technologijų, tarp jų ir lazerinės abliacijos (LA), prieinamumas paskatino ieškoti galimybių taikyti šias technologijas pacientams, sergantiems papiliniu ar folikuliniu skydliaukės vėžiu. 2021 metų Europos skydliaukės asociacijos gairės (17) ir 2022 metų Amerikos galvos ir kaklo draugijos endokrininės chirurgijos tarptautinis daugiadisciplininis konsensusas (18) teigia, kad TA procedūros galėtų būti alternatyvus gydymo metodas piktybiniam skydliaukės mazgams, taip išvengiant galimų chirurginių komplikacijų. Remiantis 2022 metų ekspertų konsensuso rekomendacijomis (19), LA siūloma skydliaukės papilinėms mikrokarcinomoms (iki 1 cm) gydyti. Vis dėlto histologinis lazerinės abliacijos poveikis skydliaukės piktybiniui mazgui, taigi ir metodo onkologinis efektas, dar nėra įvertintas ir literatūroje nėra duomenų apie tokius vykstančius registruotus tyrimus. Dėl šios



priežasties yra reikalingi tyrimai, įvertinantys LA efektyvumą ir pritaikomumą tolimesnėje klinikinėje praktikoje skydliaukės vėžio gydyme.

**Darbo tikslas:** įvertinti lazerinės abliacijos galimybes ir poveikį papilinei skydliaukės karcinomai.

**Uždaviniai:**

- 1) Įvertinti, kuriai daliai pacientų, sergančių skydliaukės vėžiu, tiktų lazerinė mazgo abliacija;
- 2) Sukurti skydliaukės naviko gyvybingumo patologinio vertinimo metodiką;
- 3) Patologinio tyrimo būdu įvertinti lazerinės abliacijos poveikį navikui;
- 4) Įvertinti lazerinės abliacijos metodo radikalumą.

## 7. TIRIAMIEJI IR METODAI

### Tiriamieji

Nuo 2023 metų vasario 14 dienos iki 2024 metų balandžio 5 dienos Vilniaus Universitetinėje ligoninėje Santaros klinikose (VUL SK) dėl įtraukimo į tyrimą buvo tikrinti pacientai, hospitalizuoti prieš numatomą skydliaukės šalinimo operaciją. Laikyta, kad pacientas gali būti įtrauktas į tyrimą, jei atitiko įtraukimo ir neįtraukimo nei vieno iš neįtraukimo kriterijų (1 lentelė).

*1 lentelė. Pacientų įtraukimo ir neįtraukimo į tyrimą kriterijai.*

Įtraukimo kriterijai:	Neįtraukimo kriterijai:
1) 18 metų ir vyresni asmenys.	1) Pacientai pagal Amerikos anesteziologų draugijos (ASA) fizinės būklės klasifikaciją įvertinti ASA > 3.
2) Paciento raštiškas sutikimas dalyvauti tyrime.	2) Pacientai, kuriems diagnozuota ne papilinė ar folikulinė karcinoma.
3) Nustatyta III-V kategorija EU-TIRADS klasifikacijoje (20) (III kategorija – žema, IV – vidutinė, V – didelė skydliaukės mazgo piktybiškumo rizika, remiantis skydliaukės echoskopinio tyrimo vaizdu).	3) Nėščios moterys.
4) Nustatyta V-VI kategorija Bethesda sistemoje (21) (V – citologiškai įtariamas, VI – patvirtintas piktybinis navikas).	
5) Naviko dydis iki 4 cm.	

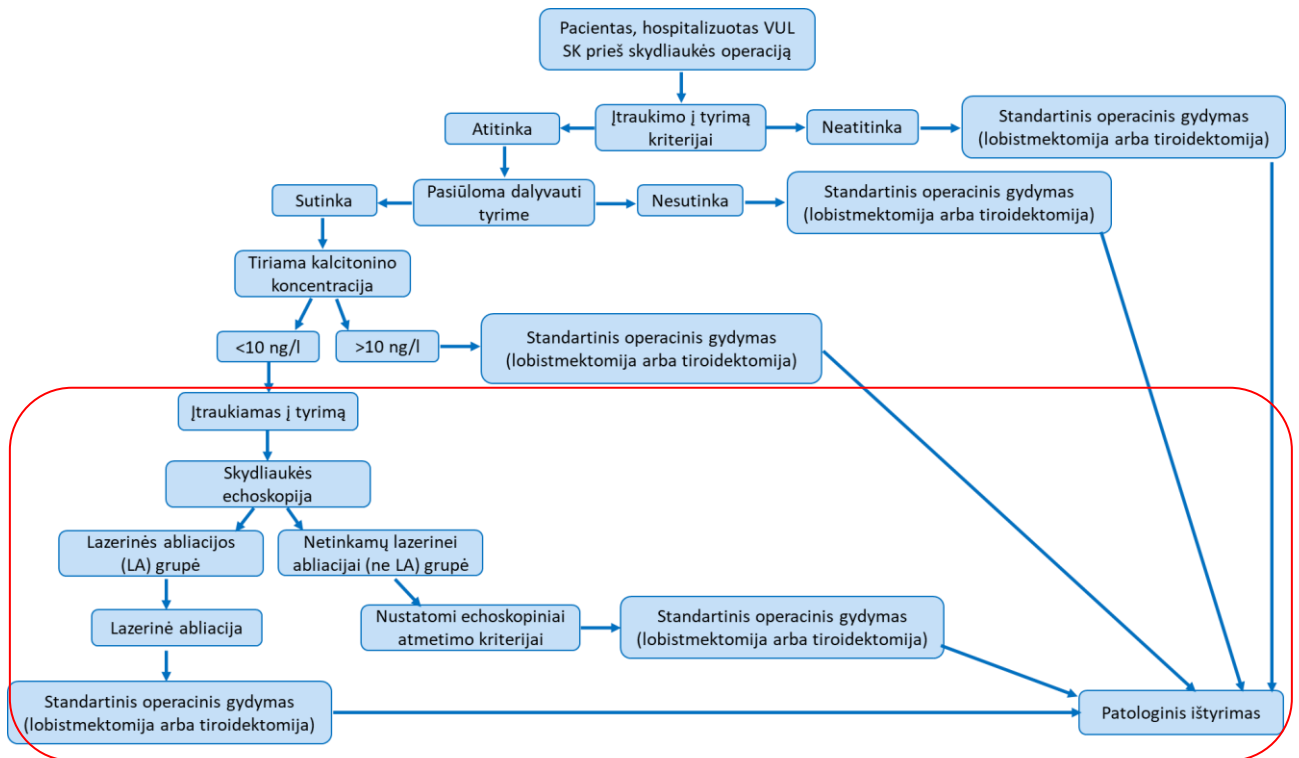
## Metodai

### Pacientų skirstymas ir lazerinės abliacijos procedūra

Pacientams, atitikusiems įtraukimo kriterijus bei nesant neįtraukimo kriterijų, buvo papildomai ištiriama kalcitonino koncentracija siekiant atmesti medulinį skydliaukės vėžį (jis įtartas, kada kalcitonino koncentracija  $>10$  ng/l). Jei kalcitonino koncentracija buvo mažiau nei 10 ng/l, pacientas buvo įtraukiamas į tyrimą (1 paveikslas) ir atliekamas papildomas echoskopinis skydliaukės ištyrimas.

Echoskopijos metu vertinama skydliaukės piktybinio mazgo dydis bei vieta (atstumas iki priekinio ir užpakalinio skydliaukės paviršių, atstumas iki viršutinio ir apatinio skydliaukės poliaus), taip pat, ar nėra trachėjos spaudimo reiškinių arba naviko invazijos į aplinkines struktūras (pagal Europos skydliaukės asociacijos gaires dėl suaugusiųjų skydliaukės mazgų piktybiškumo rizikos stratifikavimo ultragarsu (20)). Po echoskopinio tyrimo pacientas buvo priskiriamas į tinkamą lazerinei abliacijai grupę (LA grupę), kada buvo galima efektyviai ir saugiai atlikti lazerinę abliaciją aplinkinių struktūrų (trachėjos, grįžtamojo gerklų nervo, kraujagyslių) atžvilgiu, arba netinkamą lazerinei abliacijai grupę (ne LA grupę), kada buvo abejojama dėl LA efektyvumo ar buvo nesaugu dėl mazgo padėties skydliaukėje.

LA grupės pacientams, esant bendroje nejautroje prieš operacijos pradžią, echoskopijos kontrolėje paimama stulpelinė biopsija histologinei išvadai nustatyti bei atliekama mazgo LA. Abliacijos metu naudoti 18G 100 mm dydžio įvedėjai bei skaidulos (*Thyla Slim Fiber*) ir Biolitec biomedical technology GmbH lazeris – Leonardo Dual45 1064/1470nm, pasirenkant 1064 nm bangos ilgį ir nuolatinės bangos režimą (*angl. continuous wave mode*). Po lazerinės abliacijos atliekamas standartinis skydliaukės operacijos pjūvis (apie 5 cm pjūvis kaklo srityje, apie 2 cm virš jungo duobės), abliuotos skilties pusėje – klajoklio nervo 3mA neurostimuliacijos mėginys ir standartinė operacija – lobistektomija arba tiroidektomija. Nefiksuota operacinė medžiaga siunčiama patologiniam ištyrimui.



1 paveikslas. Tyrimo atlikimo schema. Raudona linija apibraukta šio klinikinio tyrimo apimtis.

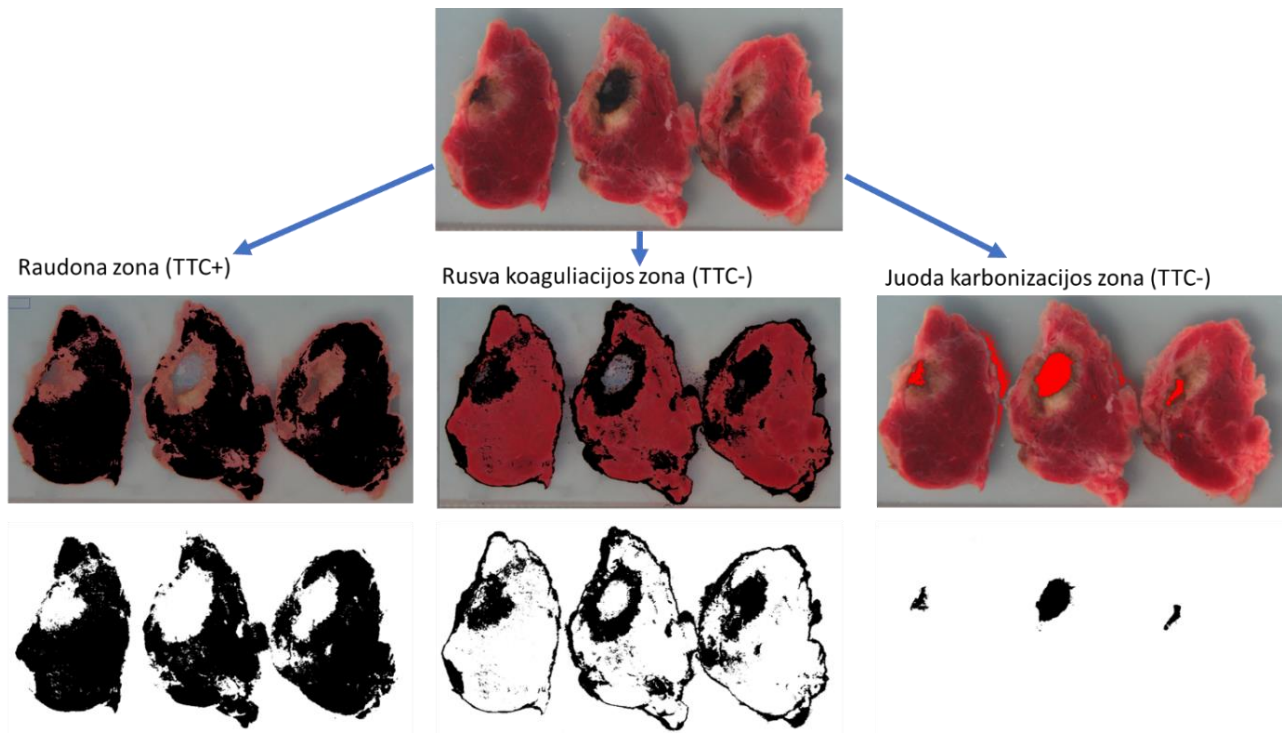
VUL SK – Vilniaus Universiteto ligoninė Santaros klinikos; LA – lazerinė abliacija.

## Patologinis ištyrimas

Skydliaukės skiltys su naviku buvo pasvertos, išmatuotos, supjaustytos serijiniais pjūviais ir nufotografuotos. Išmatuotas stebimo naviko dydis. Pacientų, kuriems buvo taikyta LA, skydliaukės audinyje išmatuota karbonizacijos zona. Skydliaukės pjūveliai su stebimais navikiniais pokyčiais buvo įmerkti į 50 ml 1.5% koncentracijos 2,3,5-trifenil-2H-tetrazolio chlorido (TTC) tirpalą. Mėginiai buvo laikomi tirpale 37°C temperatūroje 45 minutes. Po įvykusios spalvinės reakcijos, skydliaukės audiniai buvo vėl nufotografuoti.

Visa operacinė medžiaga buvo įmerkta į 10% formalino tirpalą fiksacijai. Po 24 valandų medžiaga paruošta audinių procesingui. Kiekvienas skydliaukės preparatas pagal klinikinius standartus buvo įlietas parafino bloke, supjaustytas kas 3 μm, nudažytas hematoksilino ir eozino dažais. Histologiniai vaizdai buvo įvertinti patologo bei nuskenuoti.

Skaitmeniniuose makroskopinio ištyrimo vaizduose sužymėtos ir išmatuotos zonos naudojant Fiji (Imagej) programą v.2.15. Nedažytoje medžiagoje sužymėtas balkšvas navikas, o TTC dažytoje medžiagoje pažymėta TTC-teigiama (raudonai nusidažiusi) ir TTC-neigiama (rusva bei juoda) zonos (2 paveikslas).



2 paveikslas. Skydliaukės audinys su abliuotu mazgu, dažytas TTC. Zonos suskirstytos pagal spalvinį spektrą, naudojant Fiji (Imagej) programą: kairėje – raudoną (TTC+) zoną, viduryje – rusvą koaguliacijos (TTC-) zoną ir dešinėje juodą karbonizacijos (TTC-) zoną.

TTC - 2,3,5-trifenil-2H-tetrazolio chloridas.

Skaitmeniniai histologiniai vaizdai įkelti į HALO AI programą (Indica Labs, v.3.6.4134), kurioje sužymėti ir išmatuoti naviko ir normalaus skydliaukės audinio plotai histologiniame vaizde. Navike ir normalioje parenchimoje atskirai įvertintos karbonizacijos, stiprios koaguliacijos, dalinės koaguliacijos ir nepakitusio audinio zonos. Histologiškai karbonizacijos zona apibrėžiama kaip pilno suanglėjimo zona su trapiomis, juodomis ar juosvomis masėmis ir kurioje nėra išlikusių audinių struktūrų. Karbonizuotas abliacijos kanalas ruošiant histologinį preparatą iškrinta, todėl jis į karbonizacijos ploto skaičiavimus neįtrauktas. Koaguliacijos zona traktuota kaip plotas su histologiškai stebimais architektūriniais ir citologiniais pokyčiais dėl LA sukkelto terminio efekto. Šioje zonoje esantys folikulai ir navikinės struktūros tampa deformuoti į įvairas kryptis. Koaguliuose zonose ląstelių citoplazma tampa homogeniška, neaiškių ribų, branduoliai tamsūs, smailėjantys, netaisyklingai orientuoti. Esant ryškiai struktūrų deformacijai ir citologiniams pokyčiams, koaguliacijos zona vertinta kaip neabejotina (t.y. stipri koaguliacijos zona). Jei audinyje yra stebimi ne visi koaguliaciniai pokyčiai (t.y. neryški architektūros ar ląstelių deformacija), zona vertinta kaip dalinai koaguliota. Audinys be koaguliacinių artefaktų vertintas kaip normalus.

## Statistinė analizė

Statistinė analizė atlikta naudojant R statistinės programinės įrangos paketą V 4.3.3 (© The R Foundation for Statistical Computing), RStudio 2023.12.1 Build 402 (©2009-2024 Posit Software, PBC), IBM SPSS Statistics V.23 ir G\*Power V.3.1.9.4.

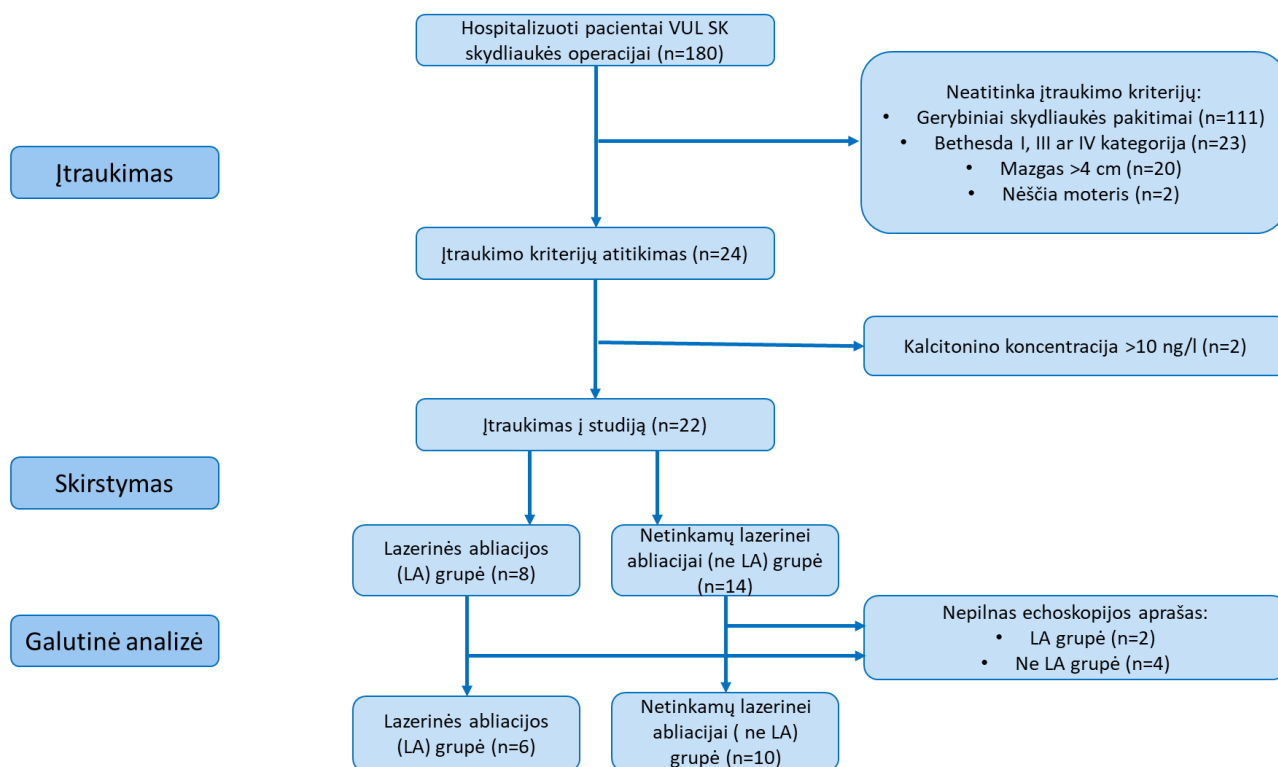
Intervaliniams ir santykiniais kintamiesiems apibūdinti naudota aprašomoji statistika: medianos su pirmaisiais (Q1) ir trečiaisiais kvartiliais (Q3), vidurkiai su standartiniu nuokrypiu (SD) bei intervalai su minimalia ir maksimalia reikšmėmis (min, max). Duomenų normalumas tikrintas naudojant Šapiro-Vilko ir Kolmogorovo-Smirnovo (K-S) testus. Nominalūs ir ordinalūs kintamieji aprašyti naudojant dažnius ir procentines dalis. Vilkoksono rangų sumų testas naudotas intervalinių kintamųjų priklausomybėms vertinti, o Pirsono Chi kvadrato testas – nominaliųjų kintamųjų priklausomybėms vertinti.

Spirmeno koreliacijos koeficientas ( $r_s$ ) buvo naudojamas siekiant nustatyti efekto dydį tarp intervalinių kintamųjų. Intervalinių kintamųjų, neatitinkančių normaliojo pasiskirstymo sąlygos, efekto dydžiui įvertinti naudotas ranginis biserinis koreliacijos efekto dydis ( $r_{rb}$ ), o ryšio stiprumui tarp nominaliųjų kintamųjų įvertinti naudotas Cramerio V ( $\phi_c$ ) efekto dydis. Poveikio dydžiai klasifikuoti pagal Funder&Ozer (2019) ("funder2019"). Poveikio dydis laikytas labai labai mažu, jei  $r_{rb}, \phi_c, r_s < 0.05$ ; labai mažu, jei  $0.05 \leq r_{rb}, \phi_c, r_s < 0.1$ ; mažu, jei  $0.1 \leq r_{rb}, \phi_c, r_s < 0.2$ ; vidutinio dydžio, jei  $0.2 \leq r_{rb}, \phi_c, r_s < 0.3$ ; dideliu, jei  $0.3 \leq r_{rb}, \phi_c, r_s < 0.4$ ; ir labai dideliu, jei  $r_{rb}, \phi_c, r_s \geq 0.4$ .

Statistiniam reikšmingumui nustatyti naudota p reikšmė, mažesnė nei 0.05 ( $p < 0.05$ ), ir statistinio tyrimo galia  $1-\beta$ , lygi 0.95 ( $1-\beta = 0.95$ ).

## 8. REZULTATAI

Nuo 2023 metų vasario 14 dienos iki 2024 metų balandžio 5 dienos buvo peržiūrėtas 180 pacientų, hospitalizuotų prieš skydliaukės operaciją, tinkamumas dalyvauti šiame tyrime. Nustatyti 46 skydliaukės vėžio atvejai, iš kurių į tyrimą galiausiai buvo įtraukta 22 pacientai. 8 įtrauktiems į tyrimą pacientams (17.4% iš visų skydliaukės vėžio atvejų) buvo taikyta LA (LA grupė) ir 14 pacientų, įtrauktų į tyrimą, buvo netinkami LA (ne LA grupė) (3 paveikslas). Į galutinę duomenų analizę buvo įtraukti 6 pacientai LA grupėje ir 10 pacientų ne LA grupėje.



3 paveikslas. Pacientų įtraukimo į tyrimą schema.

VUL SK – Vilniaus Universiteto ligoninė Santaros klinikos, LA – lazerinė abliacija.

Statistiškai reikšmingų skirtumų tarp pacientų demografinių duomenų stebėta nebuvo (2 lentelė). 94% tiriamųjų buvo moterys, vidutiniškai – 45 metų amžiaus.

2 lentelė. Demografiniai pacientų duomenys.

Rodiklis	Iš viso, N=16	LA		p-reikšmė	Efekto dydis (95% PI)
		Netinkamas, N=10	Tinkamas, N=6		
<b>Amžius</b>				0.2	-0.40 (-0.77, 0.18)
N	16	10	6		
Mediana (IQR)	41 (32, 59)	37 (29, 56)	53 (39, 64)		
Vidurkis (SD)	45 (15)	41 (14)	50 (16)		
Intervalas (min, max)	26, 67	26, 61	28, 67		
<b>Lytis</b>				>0.9	0.00 (0.00, 1.0)
Moteris	15 (94%)	9 (90%)	6 (100%)		
Vyras	1 (6.3%)	1 (10%)	0 (0%)		

LA – lazerinė abliacija; PI – pasikliautinis intervalas; IQR – tarpkvartilinis intervalas; SD – standartinis nuokrypis, min – mažiausia reikšmė; max – didžiausia reikšmė.

Lyginant abiejų grupių pacientų skydliaukės piktybinių mazgų charakteristikas, stebėtas statistiškai reikšmingai mažesnis naviko dydis LA grupėje ( $p=0.025$ ) (3 lentelė). Didelis arba labai didelis efekto dydis stebėtas lyginant atstumus iki priekinio ir užpakalinio skydliaukės paviršiaus bei viršutinio ir apatinio skydliaukės poliaus.

3 lentelė. Pacientų skydliaukės piktybinių mazgų charakteristikos.

Rodiklis	Iš viso, N=16	LA		p-reikšmė	Efekto dydis (95% PI)
		Netinkamas, N=10	Tinkamas, N=6		
<b>EU-TIRADS kategorija</b>				>0.9	0.00 (0.00, 1.0)
4	2 (13%)	1 (10%)	1 (17%)		
5	14 (88%)	9 (90%)	5 (83%)		
<b>Bethesda kategorija</b>				0.3	0.26 (0.00, 1.0)
5	9 (56%)	7 (70%)	2 (33%)		
6	7 (44%)	3 (30%)	4 (67%)		
<b>Didžiausias naviko ilgis (mm)</b>				0.025	0.70 (0.26, 0.90)
N	16	10	6		
Mediana (IQR)	15.0 (11.0, 19.0)	18.0 (14.0, 19.0)	10.0 (9.0, 11.8)		
Vidurkis (SD)	15.0 (4.9)	17.2 (4.0)	11.3 (4.0)		
Intervalas (min, max)	8.0, 23.0	11.0, 23.0	8.0, 19.0		
<b>Atstumas iki skydliaukės priekinio paviršiaus (mm)</b>				0.1	-0.40 (-0.77, 0.18)
N	16	10	6		
Mediana (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.00)	1.00 (0.00, 2.75)		
Vidurkis (SD)	0.94 (1.95)	0.30 (0.95)	2.00 (2.76)		
Intervalas (min, max)	0.00, 7.00	0.00, 3.00	0.00, 7.00		
<b>Atstumas iki skydliaukės užpakalinio paviršiaus (mm)</b>				0.064	-0.57 (-0.85, -0.04)
N	16	10	6		
Mediana (IQR)	3.00 (0.00, 5.25)	0.00 (0.00, 3.00)	4.50 (3.00, 6.75)		
Vidurkis (SD)	3.06 (3.28)	2.10 (3.31)	4.67 (2.73)		
Intervalas (min, max)	0.00, 10.00	0.00, 10.00	1.00, 8.00		
<b>Atstumas iki skydliaukės viršutinio poliaus (mm)</b>				0.4	-0.30 (-0.72, 0.28)
N	16	10	6		
Mediana (IQR)	15.5 (11.5, 20.8)	12.5 (8.5, 22.3)	16.5 (15.3, 17.8)		
Vidurkis (SD)	15.9 (6.8)	14.8 (8.1)	17.7 (3.8)		
Intervalas (min, max)	4.0, 27.0	4.0, 27.0	15.0, 25.0		
<b>Atstumas iki skydliaukės apatinio poliaus (mm)</b>				0.3	-0.35 (-0.75, 0.23)
N	16	10	6		
Mediana (IQR)	7 (0, 14)	3 (0, 11)	10 (7, 16)		
Vidurkis (SD)	9 (9)	8 (11)	11 (6)		
Intervalas (min, max)	0, 33	0, 33	4, 19		
<b>Naviko lokacija skiltyje</b>				0.34	0.00 (0.00, 1.0)
Viršutinė dalis	2 (12.5%)	2 (20%)	0 (0%)		
Vidurinė dalis	10 (62.5%)	5 (50%)	5 (83%)		
Apatinė dalis	4 (25%)	3 (30%)	1 (17%)		
<b>Trachėjos spaudimo reiškiniai</b>				>0.9	0.00 (0.00, 1.0)
Ne	15 (94%)	9 (90%)	6 (100%)		
Taip	1 (6.3%)	1 (10%)	0 (0%)		
<b>Aplinkinių struktūrų peraugimas</b>				0.3	0.26 (0.00, 1.0)
Ne	7 (44%)	3 (30%)	4 (67%)		
Taip	9 (56%)	7 (70%)	2 (33%)		

LA – lazerinė abliacija; PI – pasikliautinis intervalas; IQR – tarpkvartilinis intervalas; SD – standartinis nuokrypis, min – mažiausia reikšmė, max – didžiausia reikšmė.

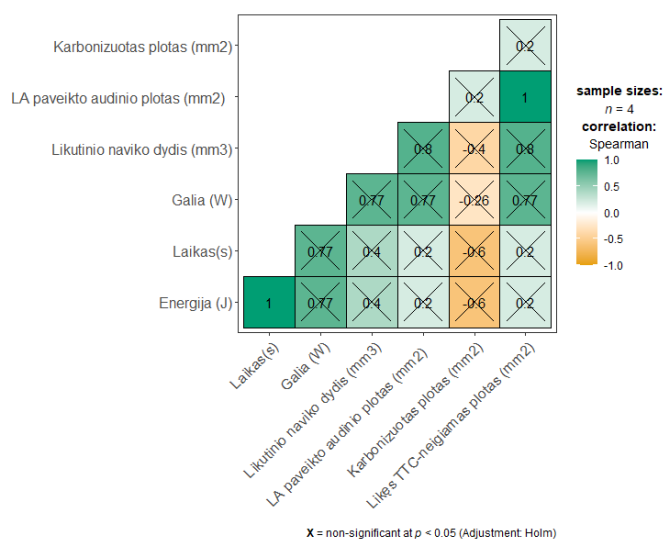
6 skydliaukės papilinės karcinomos abliuotos 3-7 W galia, suminę energiją pasiekiant daugiausiai iki 3569.1 J. Trečdaliui atvejų pasiekta pilna navikinio audinio lazerinė destrukcija, o dar trečdaliui – apskaičiuotas likutinis nepaveikto naviko plotas yra iki 1.2 mm<sup>2</sup> (4 lentelė).

4 lentelė. Lazerinės abliacijos parametų poveikio zona patologiame vertinime.

Nr	Energija (J)	Laikas (s)	Galia (W)	Karbonizacijos plotas <sup>a</sup> (visas) (mm <sup>2</sup> )	Koaguliacijos plotas <sup>a</sup> (visas) (mm <sup>2</sup> )	TTC+ naviko plotas <sup>a</sup> (mm <sup>2</sup> )	TTC+ naviko plotas <sup>a</sup> (%)	Nepaveikto naviko plotas <sup>b</sup> (mm <sup>2</sup> )	Nepaveikto naviko plotas <sup>b</sup> (%)
1	888.2	301.1	3	32.360	191.373	NA	NA	0.475	0.75
2	2701.6	563.0	5	40.809	383.235	NA	NA	0.000	0.00
3	1547.0	399.6	5	15.63	61.668	0.00	0.00	1.204	16.63
4	3088.5	624.4	5	2.653	21.935	7.469	39.42	8.463	38.26
5	1272.1	260.3	5	8.014	41.171	0	0.00	0.000	0.00
6	3569.1	647.7	7	0.009	19.941	2.867	1.95	76.121	69.67

Visas – naviko zona+skydliaukės parenchimos zona; TTC - 2,3,5-trifenil-2H-tetrazolio chloridas; NA – netaikoma; nepaveikto naviko plotas – likutinis histologiškai identifikuojamas naviko plotas; <sup>a</sup> – makroskopinis vertinimas, <sup>b</sup> – mikroskopinis vertinimas.

Nustatyta stipri tiesioginė, statistiškai reikšminga koreliacija tarp laiko ir suminės LA energijos (4 paveikslas). Stipri tiesioginė koreliacija taip pat matoma tarp galios ir LA paveikto audinio ploto (karbonizuoto ploto ir likusio TTC-neigiamo ploto sumos) bei silpna atvirkštinė koreliacija tarp galios ir karbonizacijos ploto atskirai, tačiau abi koreliacijos šiuo, mažos imties dydžio, atveju yra statistiškai nereikšmingos. Komplikacijų (intraoperacinių ir pooperacinių) dėl LA nebuvo, visi klajoklio nervo neurostimuliacijos atsakai buvo išgauti.

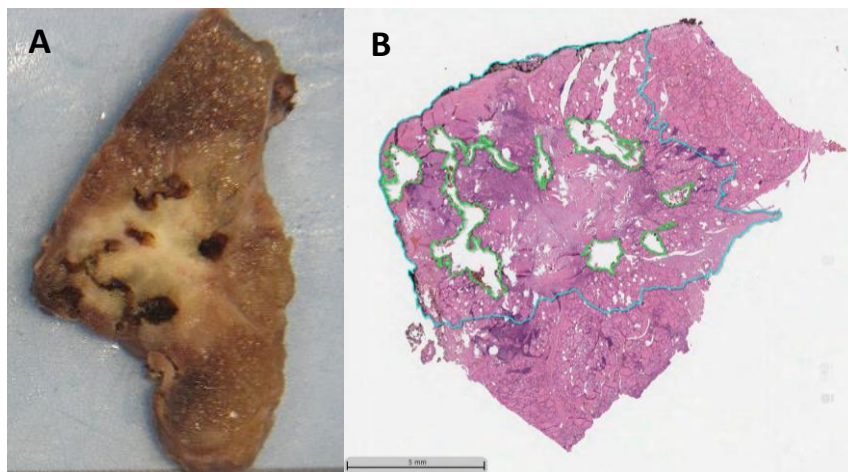


4 paveikslas. Koreliacijos tarp lazerinės abliacijos parametų ir poveikio zonos.

LA – lazerinė abliacija; TTC - 2,3,5-trifenil-2H-tetrazolio chloridas.

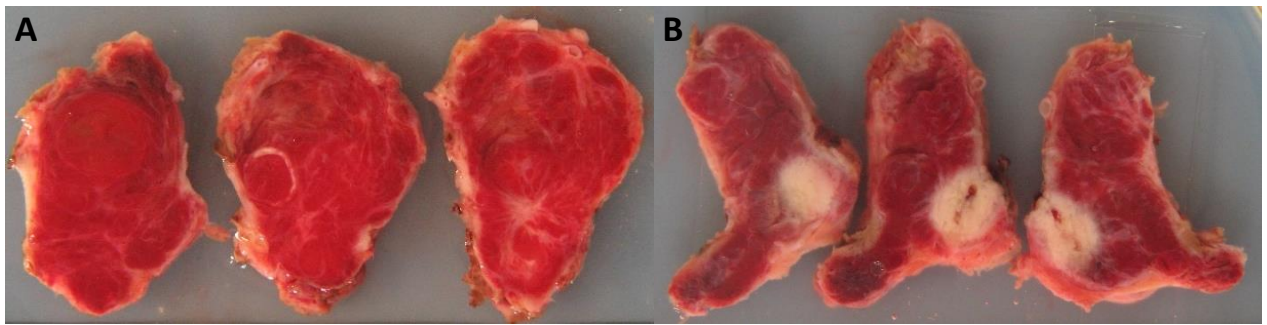


Po tiroidektomijos histologiškai vertinant abliuotas skydliaukes, buvo stebėta karbonizacijos zona, kai kuriais atvejais su abliacijos kanalu ar kanalais viduje, ir koaguliacijos zona. Karbonizacijos zonoje neliko ląstelės struktūrų, tuo tarpu koaguliacijos zonoje liko pakitusios naviko ląstelės, kurių gyvybingumo, dažant hematokslinu ir eozinu, neįmanoma įvertinti. Už LA paveiktų struktūrų buvo matomas nepakitęs skydliaukės audinys (5 paveikslas).



5 paveikslas. Skydliaukės naviko po lazerinės abliacijos makroskopinis (A) ir mikroskopinis (B) vaizdai: žalia linija riboja karbonizacijos zoną (makroskopiniame vaizde – juodos/juosvos spalvos zonos), mėlyna – koaguliacijos zoną su pakitusiomis naviko ląstelėmis, o skydliaukės plotas už mėlynos linijos – nepakitęs skydliaukės audinys.

TTC dažai buvo validuoti tik po pirmųjų lazerinių skydliaukės vėžio abliacijų, stebint neaiškaus gyvybingumo koaguliacijos zoną histologiniame vaizde. Paskutinės 4 abliuotos ir 4 neabliuotos skydliaukės su papiline karcinoma buvo dažytos TTC dažais. Neabliuotos skydliaukės atveju – piktybinis mazgas ir aplinkiniai skydliaukės audiniai buvo TTC-teigiami (dažėsi raudona spalva). Abliuotas skydliaukės navikas buvo TTC-neigiamas (balkšvas), aplink jį – LA nepaveiktas skydliaukės audinys, kuris buvo TTC-teigiamas (dažėsi raudona spalva) (6 paveikslas). Abejose grupėse skydliaukės skilties rezekcijos kraštas bei fibrozinės septos navike ar skydliaukės audinyje buvo TTC-neigiami (išliko balkšvi). Neabliuotas navikas statistiškai patikimai dažosi raudona spalva – yra TTC-teigiamas, lyginant su abliuotu TTC-neigiamu navikiniu audiniu ( $p=0.029$ ) (5 lentelė).



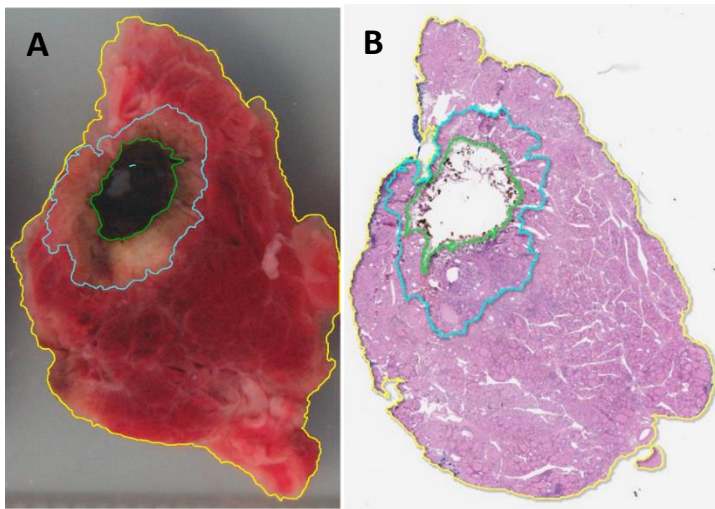
6 paveikslas. A – neabliuotas TTC dažytas skydliaukės mazgas, B – abliuotas TTC dažytas skydliaukės mazgas. A – skydliaukės mazgas ir aplinkinė skydliaukės parenchima TTC-teigiami (dažosi raudona spalva), B – abliuotas skydliaukės mazgas – TTC-neigiamas (balkšvas), aplink – LA nepaveiktas TTC-teigiamas skydliaukės audinys. TTC – 2,3,5-trifenil-2H-tetrazolio chloridas.

5 lentelė. Naviko ir skydliaukės parenchimos teigiama reakcija su 2,3,5-trifenil-2H-tetrazolio chloridu tarp abliuotų ir neabliuotų pacientų grupių.

Rodiklis	Abliuoti navikai, N=4	Neabliuoti navikai, N=4	p-reikšmė	Efekto dydis (95% PI)
<b>TTC+ naviko plotas (mm<sup>2</sup>)</b>			0.029	-1.0 (-1.0, -1.0)
N	4	4		
Mediana (IQR)	1 (0, 4)	185 (173, 207)		
Vidurkis (SD)	3 (4)	195 (50)		
Intervalas (min, max)	0, 7	146, 266		
<b>TTC+ normalaus audinio plotas (mm<sup>2</sup>)</b>			0.7	0.25 (-0.53, 0.80)
N	4	4		
Mediana (IQR)	531 (390, 634)	280 (262, 366)		
Vidurkis (SD)	493 (355)	349 (168)		
Intervalas (min, max)	24, 887	237, 599		

PI – pasikliautinis intervalas; TTC+ – teigiama reakcija su 2,3,5-trifenil-2H-tetrazolio chloridu; IQR – tarpkvartilinis intervalas; SD – standartinis nuokrypis, min – mažiausia reikšmė, max – didžiausia reikšmė.

Lyginant TTC neigiamą zoną makroskopiniame vaizde su LA sukelta koaguliacijos zona mikroskopiniame vaizde, matoma, jog TTC neigiama zona apima histologiškai stebimus architektūrinius ir citologinius navikinių ląstelių pakitimus (7 paveikslas). Tai indikuoja lazerinės abliacijos paveiktų ląstelių žūtį. LA nepaveikto navikinio audinio plotas buvo TTC-teigiamas ir išlaikė histologiškai nepakitusias naviko struktūras.



7 paveikslas. A – makroskopinis, B – histologinis skydliaukės su abliuotu mazgu vaizdas. Žalios spalvos linija riboja karbonizacijos plotą, mėlynos spalvos – A vaizde TTC-neigiamą zoną ir B vaizde – koaguliacijos zoną, geltonos spalvos – nepakitusių skydliaukės audinį. TTC – 2,3,5-trifenil-2H-tetrazolio chloridas.

## 9. APTARIMAS

### Literatūros šaltiniai ir paieškos strategija

Darbe naudoti informacijos šaltiniai ieškoti PubMed, MEDLINE ir Cochrane Library internetinėse duomenų bazėse iki 2024 metų kovo mėnesio. Paieškose buvo naudojami šie raktiniai žodžiai ar jų deriniai: „thyroid cancer“, „papillary thyroid carcinoma“, „laser ablation“, „thermal ablation“, „treatment“, „triphenyl tetrazolium chloride“, „cell viability“ ir „viability assay“.

### Aptarimas

Šio tyrimo duomenimis – LA įmanoma 17.4% pacientų su skydliaukės vėžiu. Atlikus makroskopinį ir mikroskopinį abliuotos skydliaukės skilties tyrimą, buvo nustatyta LA sukelta mazgo centrinė karbonizacijos bei aplinkinė, koaguliacijos zona, kurios buvo TTC neigiamos. Nepaveiktas audinys išlaikė normalią histologiją ir buvo TTC-teigiamas. Turimomis žiniomis tai yra pirmasis tyrimas, kuriame patologiniais tyrimo metodais įvertintas lazerinės abliacijos metodo radikalumas.

Nors naujų diagnozuojamų atvejų skaičius paskutiniaisiais dešimtmečiais auga, mirštamumas dėl skydliaukės vėžio išlieka sąlyginai nedidelis, o ligos progresavimas lėtas. Didžiausias sergamumas fiksuojamas aukšto išsivystymo, o mirtingumas neproporcingai didesnis – tik žemo išsivystymo šalyse (3). Tai susiję su sveikatos priežiūros paslaugų prieinamumo skirtumais ir aplinkos poveikiu, pavyzdžiui, jonizuojančia spinduliuote ir jodo trūkumu. Pasaulyje diferencijuotas skydliaukės vėžys, įskaitant papilinį ir folikulinį skydliaukės vėžį, yra dažniausias tipas ir sudaro daugiau kaip 90% visų atvejų. Jų prognozė puiki, o pacientų, gydytų dėl diferencijuoto skydliaukės vėžio, gyvenimo trukmė nedaug skiriasi nuo bendros populiacijos (26). Apie 50% iš diferencijuotų skydliaukės vėžių yra papilinės skydliaukės mikrokarcinomos, kurių pagal Pasaulio Sveikatos Organizacijos skydliaukės

navikų klasifikacijos apibrėžimą didžiausias skersmuo yra mažesnis nei 10 mm (27,28). Dėl indolentinio jų pobūdžio tradicinis chirurginis gydymas tinka ne visiems pacientams, nes kyla komplikacijų, chirurginio rando, skydliaukės funkcijos praradimo ir neigiamo poveikio gyvenimo kokybei rizika. Dėl šių priežasčių pacientams, sergantiems skydliaukės papiline mikrokarcinoma, nuo 1990 metų Japonijoje buvo pasiūlyta taikyti aktyvų stebėjimą kaip alternatyvią strategiją operacijai (25,26). Meta-analizės duomenimis, aktyvų stebėjimą pasirinkusių asmenų fizinio gyvenimo kokybė pagerėjo (31). Vis dėlto yra nemažai aktyvaus stebėjimo trūkumų, įskaitant būtinybę visą gyvenimą stebėti ultragarsu ir padidėjusį pacientų nerimą dėl žinojimo, kad liga išlieka. Kohortiniame tyrime buvo nustatyta, jog, pasirinkus tik stebėjimo taktiką, skydliaukės mazgo dydis padidėjo iki 5% atvejų, apie 1.5% pacientų atsirado metastazių limfmazgiuose ir apie 3.5% pacientų pasireiškė klinikinės ligos progresavimas (32). Taigi aktyvus naujai diagnozuotų pacientų stebėjimas, su nors ir lėtai progresuojančia liga, gali vesti iki daug agresyvesnio chirurginio gydymo nei pirminės diagnozės nustatymo metu.

Yra vis daugiau įrodymų, kad TA metodai, įskaitant LA, yra veiksmingi ir saugūs gerybinių skydliaukės mazgų ir recidyvuojančio skydliaukės vėžio gydymo būdai (33). Dėl to pacientams su nustatyta papiline karcinoma, kurie atsisako operacijos, bet nesutinka su aktyvaus stebėjimo strategija, arba kurie negali operuotis dėl gretutinių būklių, vis dažniau siūlomas nechirurginis TA gydymas. LA tinkamumas pasaulyje vertintas žemos rizikos papilinės karcinomos (34), daugiažidininės papilinės karcinomos gydymui (31), taip pat gydant atsinaujinančią papilinę skydliaukės mikrokarcinomą (32). Pacientai po LA buvo sekami, jiems nebuvo stebima naviko recidyvo, metastazių limfmazgiuose ar atokiųjų metastazių. Taip pat statistiškai reikšmingai sumažėjo tiroglobulinų koncentracija po lazerinės naviko abliacijos (37). Po gydymo LA nebuvo stebėta jokių didžiųjų komplikacijų (37,38) arba jos buvo retos (<1%) (35), o komplikacijų rizika yra žymiai didesnė pakartotinai atliekant atvirą operaciją kakle dėl ligos atsinaujinimo ar metastazių kaklo limfmazgiuose po skydliaukės ar jos dalies pašalinimo operacijos (40,41). Taigi po buvusios operacijos, TA gydymo būdai, įskaitant LA, yra saugesnis pasirinkimas dėl susidariusios pooperacinės audinių fibrozės.

Pastarųjų metų studijos pateikia daugiau rezultatų apie vis platesnį, saugų ir efektyvų LA taikymą skydliaukės mikrokarcinomų gydymui. Meta-analizė, nagrinėjusi 2014-2020 metų publikacijas, lyginančias TA (įskaitant LA) metodus ir chirurginį papilinės skydliaukės mikrokarcinomos gydymą, pateikia išvadas, jog abu minėti gydymo variantai pasižymi panašiu efektyvumu ir saugumu, o išeitys, pacientus sekant 12 mėnesių, statistiškai reikšmingai nesiskyrė tarp šių grupių (38). Be to, TA gydymo metodų operacijos bei hospitalizacijos trukmė ir komplikacijų dažnis buvo reikšmingai mažesnis nei chirurginės grupės. Taip pat apskaičiuota, kad LA, palyginus su chirurginiu gydymu, yra ekonomiškai efektyvus gydymo metodas tiek gerybinių, tiek piktybinių pakitimų atveju (44). Naujausia meta-

analizė, apibendrinusi tyrimus iki 2022 metų, taip pat nenustatė statistiškai reikšmingų skirtumų tarp LA ir kitų TA (mikrobangų abliacijos ir radiodažnuminės abliacijos) veiksmingumo ir saugumo, atlikus bent 6 mėnesių stebėjimo analizę (40). Kita vertus, skydliaukės papildinis vėžys yra labai lėtai progresuojantis navikinis susirgimas (41), todėl 6 ar 12 mėnesių sekimas minėtose studijose nėra pakankamas išvadoms dėl tolimųjų išeičių daryti. Kita sisteminė apžvalga teigia, kad onkologiniu požiūriu LA yra tiek pat efektyvi kaip standartinis gydymas (tiroidektomija ar lobistmektomija) (42), tačiau onkologinis efektas šioje studijoje grįstas taip pat tik pooperaciniu paciento sekimu. Mūsų atlikto pilotinio tyrimo duomenimis LA metu tik trečdaliui pacientų pasiekama pilna navikinio audinio destrukcija. Mūsų duomenys yra grįsti abliuoto skydliaukės mazgo patologinio tyrimo rezultatais. Kitame tyrime LA onkologinis efektas grindžiamas pacientus vertinant praėjus 1 ir 12 mėnesių po LA (47). Jiems atliekama plonos adatos aspiracinė biopsija bei nustatoma ląstelių nekrozė ir uždegiminės ląstelės be gyvybingų navikinių ląstelių. Vis dėlto literatūros duomenimis apie 40% atvejų citologinis tyrimas nėra pakankamai jautrus nustatyti skydliaukės vėžio ląsteles (9–11). Taigi patologinis LA efektas ir radikalumas atliktose studijose pasaulyje vis dėlto nėra ištirtas. Tai buvo įvertinta mūsų tyrime po LA atliekant operaciją – tiroidektomiją ar lobistmektomiją, bei pritaikant TTC dažus ląstelių gyvybingumui vertinti. Literatūros duomenimis TTC gali patvirtinti ankstyvą, makroskopiškai bei histologiškai, dažant hematoksilinu ir eozinu, dar nematomą audinio žūtį (22,23). TTC yra bespalvis, vandenyje tirpus dažiklis, kurį gyvų ląstelių mitochondrijų fermentas sukcinato dehidrogenazė redukuoja į vandenyje netirpų junginį (formazaną), kuris sveikus ir normalius audinius nudažo raudona spalva, todėl teigiama TTC reakcija yra stebima tik gyvose ląstelėse. Fibrozės sritį sudaro kolageno skaidulos, kurios neturi fermento sukcinato dehidrogenazės, taigi TTC negali būti redukuojamas į formazaną ir dėl to fibrozės zonos, esančios navike, susiformavusios po biopsijos ar esančios normalioje skydliaukės parenchimoje, taip pat kaip išeminės sritys, lieka TTC-neigiamos (24,25). Literatūroje iki šiol TTC taikytas tik širdies ar smegenų ūmios išemijos plotams nustatyti, tačiau nėra duomenų apie TTC naudojimą skydliaukės audinio gyvybingumo vertinimui. Po pirmųjų histologinių rezultatų su neaiškios gyvybingumo zona, TTC dažai buvo iš pradžių validuoti skydliaukės audiniui, bandymus atliekant ant sveikų ir su gerybiniais hiperplastiniais mazgais skydliaukės mėginių. Tuomet TTC dažymas buvo įtrauktas į metodiką kompleksiniam patologiniam papildinių skydliaukės karcinomų vertinimui kartu su histologiniu vaizdu.

LA terminis poveikis audiniui mažėja tostant nuo lazerio skaidulos įvedimo vietos – šilumos šaltinio. Tas atsispindi ir audinių histologiniuose vaizduose, kur perėjimas nuo normalaus (t.y. LA nepaveikto) audinio link LA paveikto audinio yra subtilus. Artėjant link šilumos šaltinio, pokyčiai tampa vis labiau akivaizdesni, o centrinėje dalyje matomi sudeginto audinio likučiai. Dėl to šiame tyrime buvo pasirinkta koaguliacijos zoną išskaidyti į dvi dalis. Stiprios koaguliacijos zona nurodo į akivaizdžius LA padarytus pokyčius audiniui ir, kartu su neigiama TTC reakcija toje pačioje zonoje – į negrįžtamus

pokyčius ląstelėse. Dalinai koaguluotoje zonoje audiniai nėra tiek deformuoti kiek stipriai koaguluotoje zonoje, tačiau tai yra LA padarinys, kurio reakcija buvo taip pat TTC-neigiama, taigi, tikėtina, kad dalinai koaguluota zona taip pat atspindi negrįžtamus pokyčius audiniuose. Karbonizuotoje zonoje nėra išlikusių audinių histologinių struktūrų. Dėl šios priežasties karbonizacijos zonai esant tarp navikinių ir sveikų audinių arba rezekcijos krašte, negalima įvertinti tik naviko karbonizacijos ploto. Karbonizacijos zona atspindi stipriausią LA efektą skydliaukės navikiniam ir normaliam audiniui.

LA grupėje atkreiptinas dėmesys į dviejų pacientų mazgų abliacijas, išsiskyrusias iš likusių. Vienu atveju (paciento nr.4) – 39% likutinio naviko ploto dažėsi TTC-teigiamai. Pažymėtina, kad ultragarsinio tyrimo metu didžiausias išmatuotas naviko matmuo buvo 8 mm, o makroskopinio tyrimo metu po abliacijos stebėtas likutinis navikas buvo 5.5 mm. Lazerio skaidula buvo mazgo krašte, dėl to likusi minimali karbonizuota zona ( $2.7 \text{ mm}^2$ ) buvo taip pat navikinio audinio krašte. Šalia skaidulos įvedimo vietos – naviko TTC neigiama zona apėmė  $11.5 \text{ mm}^2$  plotą. Atokiausiai nuo skaidulos buvusio naviko zona ( $7.5 \text{ mm}^2$ ) turėjo teigiamą TTC reakciją, o tame plote histologiškai stebėtas fibrozuotas nepaveiktas navikas, kas galėjo lemti apsunkintą naviko abliaciją ir nepakankamą LA efektą, nepaisant nedidelio mazgo dydžio. Antru atveju (paciento nr.6) – stebėta 2% teigiamai TTC besidažančio naviko zona, tačiau mikroskopiškai nustatyta 70% nepaveikto navikinio ploto. Histologiškai tarp navikinių ląstelių stebimi gausūs fibrozės plotai, kurie dažosi TTC neigiamai, bet jie yra apsupti navikinių ląstelių, todėl įeina į apskaičiuotą mikroskopinį nepaveikto naviko plotą. Vertinant kompleksiskai, galima interpretuoti, kad 2% teigiamai TTC besidažančio naviko ir yra likęs nepaveiktas tarp fibrozės zonų išsidėstęs naviko plotas. Abiem atvejais LA buvo apsunkinta, navikai buvo kietesni nei kiti abliuoti mazgai, o abliacijos matomiems pakitimams ultragarsiniame vaizde pasiekti prireikė aukštesnių nei iki tol naudotų parametru, kada bendra energija abiem atvejais viršijo 3000 J. Vertinant kartu LA ir patologinio ištyrimo duomenis, nustatyta, kad apsunkinta, aukštesnių parametru reikalaujanti LA yra fibrozuotų navikų atvejais.

Literatūroje yra įvairių duomenų dėl optimalių parametru skydliaukės mazgo lazerinei abliacijai. Lazerinės abliacijos tyrimai su kiaulės skydliaukės modeliais *ex vivo* siūlo 10-12 mm LA poveikio zonai išgauti 3 W galią ir 1800 J energiją (48). Pažymėtina, kad šie bandymai atlikti ant sveiko skydliaukės audinio, kurio struktūra yra visiškai kitokia nei naviko atveju. 2022 metų ekspertų konsensusas dėl LA taikymo papilinės skydliaukės mikrokarcinomos gydymui (19) taip pat, remdamiesi eksperimentiniais duomenimis, siūlo skydliaukės papilines karcinomas abliuoti 3-3.5 W lazerio galia, iki suminės 1800 J energijos. Tik jei mazgeliai yra kietos tekstūros ir Hashimoto tiroidito fone, procedūros pradžioje galima naudoti didesnę galią (4.5-5.5 W), o kai echoskopiniame vaizde pradeda formotis abliacijos zona – galią sumažinti iki 3.0-3.5 W. Konsensusas taip pat apibendrina, kad didėjant galiai ir energijai, lazerio abliacijos poveikis palaipsniui didėja iki 1800 J energijos (tarp

abliacijos apimties ir įvestos energijos yra beveik tiesinė priklausomybė), tačiau bet koks tolesnis energijos tiekimas, viršijantis šią ribą, lemia ribotą abliacijos apimties didėjimą. Mūsų tyrime stebėta stipresnė galios ir abliacijos zonos teigiama koreliacija. Taip pat nustatyta, kad didinant LA galią, mažėja karbonizacijos plotas dėl tikėtino skaidulos apanglėjimo, bet daugeliu papildinių karcinomu atveju efektyvus LA efektas ultragarsiniame vaizde stebėtas visos LA metu išlaikant aukštesnę nei 3W galią. Mūsų tyrimo duomenimis – fibrozuotiems navikams yra reikalinga didesnė suminė energija nei yra rekomenduotina (>3000 J), siekiant matomų LA pokyčių ultragarsiniame vaizde. Patologinio tyrimo duomenimis – LA poveikis stipriai fibrozuotiems navikams vis dėlto nėra pakankamas pilnai mikroskopinio navikinio audinio destrukcijai pasiekti. Šiuo metu trūksta preoperacinių tyrimų duomenų, padedančių identifikuoti LA tinkamus nefibrozuotus navikus, o fibrozė navike nustatoma tik histologinio ištyrimo metu. Taigi reikalinga suminė energija navikiniam mazgui turi būti apsprendžiama LA atliekančio klinicisto pagal procedūros metu matomus pokyčius ultragarsiniame vaizde.

Klinikinėje praktikoje trūksta kriterijų, padedančių nuspręsti, ar pacientas, sergantis skydliaukės papiline karcinoma, yra tinkamas LA procedūrai, ar ne. Remiantis konsensuso dėl mikrokarcinomų LA duomenimis, LA yra tinkami tie pacientai, kuriems nenustatyta navikinės ekstratiroidinės invazijos į kaklo limfmazgius ar raumenis bei kurių mazgas yra bent 1-2 mm nutolęs nuo skydliaukės kapsulės (19). Mūsų tyrime netinkamų LA pacientų grupė nuo neabliuotų skydliaukės mazgų grupės statistiškai reikšmingai išsiskyrė tik dėl vidutiniškai 5.9 mm mažesnio naviko dydžio ( $p=0.025$ ). Šiame tyrime buvo įtraukiami pacientai, kuriems diagnozuota ne tik mikrokarcinoma, bet ir iki 4 cm dydžio papildinis skydliaukės navikas. Didžiausias abliuotas mazgas LA grupėje buvo 19 mm dydžio bei buvo pasiekta pilna jo destrukcija (be likutinio nepaveikto naviko ploto histologiniame vaizde), taip įrodant galimybę LA taikyti ir didesniems nefibrozuotiems navikams. Vis dėlto pažymėtina, kad šiame tyrime taip pat stebimas didelis efekto dydis, lyginant grupes pagal naviko atstumą iki priekinio skydliaukės paviršiaus, taip pat iki viršutinio ir apatinio poliaus, bei labai didelis efekto dydis – lyginant grupes pagal atstumą iki skydliaukės užpakalinio paviršiaus. Tai reiškia, kad minėti echoskopiniai kriterijai skiriasi tarp grupių ir skirtumai yra svarbūs klinikinėje praktikoje, skirstant pacientus į tinkamų ir netinkamų LA grupes, tačiau šių rodiklių p-reikšmė tarp grupių yra statistiškai nereikšminga dėl nedidelės imties. Pakartotinis vertinimas, tyrimą tęsiant su didesne pacientų imtimi, tikėtina, pagrįstų šių charakteristikų statistinį reikšmingumą.

Šis tyrimas padeda įvertinti platesnio LA įvedimo į praktiką galimybes, ištyrus onkologinį LA efektą. Vis dėlto tyrimas taip pat turi ir ribotumą: 1) imtis yra maža; 2) tyrime nagrinėtos grupės yra nelygios. Šie ribotumai yra susiję su pilotinio tyrimo dizainu, kadangi buvo vertintas LA metodo efektyvumas abliuojant skydliaukės vėžį. Taip pat TTC spalvinė reakcija ar koaguliaciniai pokyčiai atskirai nėra

tiesioginiai ląstelės žūties įrodymai, todėl negrįžtamų LA pokyčių pagrindimui yra būtinas kompleksinis patologinis vertinimas.

## 10. IŠVADOS IR PASIŪLYMAI

### Išvados

- 1) Lazerinė abliacija yra įmanoma 17.4% pacientų, sergančių skydliaukės vėžiu.
- 2) Hematoksilino ir eozino dažai negali įvertinti koaguliacijos zonos navikinių ląstelių gyvybingumo, o skydliaukių audiniui validuotas 2,3,5-trifenil-2H-tetrazolio chloridas rodo šių ląstelių žūtį.
- 3) Lazerinė abliacija sukelia naviko struktūros pakitimus, matomus tiek makroskopiškai, tiek histologiškai: karbonizacijos bei koaguliacijos zonas, tačiau dalyje mėginių stebimi nepakitusio naviko plotai.
- 4) Lazerinė abliacija yra tik trečdaliu atvejų radikalus skydliaukės vėžio gydymo metodas.

### Pasiūlymai

Šiuo tyrimu su nedidele tiriamųjų grupe buvo vertintas LA efektyvumas gydant skydliaukės vėžį. Tęsiant tyrimą, rezultatų tikslumą dar padidins planuojama didesnė tiriamųjų imtis bei numatomas papildomas imunohistocheminis ištyrimas, siekiant tiksliai identifikuoti likutinį gyvybingą naviko audinį. Norint įsitikinti pilna naviko žūtimi po LA, vertėtų makroskopinius bei histologinius parametrus vertinti kartu, kompleksiskai, įtraukiant imunohistocheminius tyrimus bei pacientų tolimesnę sekimą dėl galimo naviko recidyvo.

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## **PASTABOS**

Lietuvos mokslų akademijos prezidiumas už mokslo darbą „Lazerinė abliacija skydliaukės papilinės karcinomos gydyme: nuo eksperimentinio tyrimo iki klinikinės studijos“ skyrė 2023 m. Lietuvos mokslų akademijos Aukštųjų mokyklų studentų mokslinių darbų premiją (žr. 26 lapą).

Taip pat tyrimo rezultatai buvo pristatomi tarptautinėse konferencijose (žr. 27-32 lapus):

- 1) „The first experience of laser ablation as an alternative treatment for thyroid cancer” – Baltijos šalių onkologų ir chirurgų kongrese (*angl. Baltic congress of oncologists and surgeons*), 2023.09.17-18, Taline, Estijoje. Gauta geriausios santraukos nominacija.
- 2) „Laser ablation applicability in treatment of thyroid cancer: ongoing trial” – 10-ajame Europos endokrininių chirurgų draugijos kongrese (*angl. 10th Biennial Congress of European Society of Endocrine Surgeons*), 2024.05.23-25, Romoje, Italijoje.

Toliau taip pat pridedami studijų laikotarpiu išspausdinti **straipsniai** (33-99 lapai).

LIETUVOS  
MOKSLŲ AKADEMIJOS  
PREZIDIUMAS  
*skiria*

magistrei Kristinai Marcinkevičiūtei

Vilniaus universitetas

už mokslo darbą

*Lazerinė abliacija skydliaukės papilinės karcinomos gydyme:  
nuo eksperimentinio tyrimo iki klinikinės studijos*

darbo vadovas prof. dr. Tomas Poškus

2023 m. Lietuvos mokslų akademijos  
Aukštųjų mokyklų studentų  
mokslinių darbų premiją

Prezidentas Jūras Banys

2024 m. sausio 9 d.

VILNIUS

Nr. 10

## Results

Our University Hospital's endocrine surgery unit reported a higher proportion of papillary thyroid carcinoma (PTC) cases (87%) compared to the Eurocrine registry (84.4%). Follicular thyroid carcinoma (FTC) accounted for 5.8% in our unit and 6.2% in Eurocrine, while medullary thyroid carcinoma (MTC) represented 4.5% and 3.8%, respectively. Lymph node dissections performed in our unit aligned with Eurocrine, encompassing central and lateral neck dissections based on preoperative findings. Analysis of the types of operations performed revealed similarities between our unit and Eurocrine. Both datasets included total thyroidectomy and hemithyroidectomy as the primary surgical approaches for thyroid cancer. Parathyroidectomy was performed for parathyroid cancer cases in both datasets as well. Postoperative complications, including RLN palsy, parathyroid insufficiency, and reoperation due to hematoma, showed comparable rates between our unit and Eurocrine. This indicates alignment in surgical management and techniques, leading to similar complication rates.

## Conclusions

This comparative analysis between our university hospital's endocrine surgery unit and the Eurocrine registry sheds light on neck oncological endocrine surgery trends and outcomes. Although slight variations in the distribution of thyroid cancer subtypes were observed, overall surgical approaches, including lymph node dissections and types of operations performed, aligned with European practices. Similar postoperative complication rates imply that our unit's techniques and perioperative care adhere to European standards. These findings contribute to the understanding of endocrine surgical practices, supporting ongoing improvements and standardization in this specialized field.

## Brief description of the abstract

This study compares neck oncological endocrine surgery at a University Hospital with the European registry Eurocrine. Analysis shows alignment in cancer subtypes, operations, lymph node dissections, and complications. Findings underscore the importance of international surgical registries, especially for small countries, enabling benchmarking and enhancing endocrine surgical practices.

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### P-03 The first experience of laser ablation as an alternative treatment for thyroid cancer

Track: Endocrine surgery

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- 2) Donatas Jocius\*, Faculty of Medicine, Vilnius University; Vilnius University Hospital Santaros Klinikos, Center of radiology and nuclear medicine, Lithuania
- 3) Augustas Beiša, Faculty of Medicine, Vilnius University; Center of Abdominal and Oncosurgery, Vilnius University Hospital Santaros Klinikos, Lithuania
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- 9) Tomas Poškus, Faculty of Medicine, Vilnius University; Center of Abdominal and Oncosurgery, Vilnius University Hospital Santaros Klinikos, Lithuania

## Objective

Over recent decades, there has been an increasing interest in thyroid cancer treatment approaches. International publications and treatment guidelines recommend the use of active surveillance instead of aggressive surgery for low-risk tumours. However, the patient's quality of life is impaired by the diagnosis of an oncological disease that is simply monitored. As a result, alternative treatments are constantly being sought to improve the patient's outcome and quality of life. The increasing availability of thermal ablation technologies such as laser ablation, which is successfully used in other malignant lesion treatment, has encouraged the exploration of the feasibility of applying these technologies to patients with thyroid cancer. The European Thyroid Association guidelines and an international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section, published in 2021, indicate that thermal ablation procedures could be an alternative treatment method for malignant thyroid nodules, avoiding surgical complications or hypothyroidism. According to the recommendations of the 2022 Expert Consensus on the use of laser ablation in the treatment of papillary thyroid microcarcinoma, laser ablation is indicated for small papillary thyroid carcinomas due to the precision of the laser ablation, the complete destruction of the tumour and the safety of the procedure. The aim of this study is to evaluate the feasibility and histological effect of laser ablation in patients with thyroid carcinoma.

## Methods

Vilnius Regional Ethics Committee in February 2023 gave permission (No. 2023/2-1481-958) to conduct the experimental study. Patients, who were 18 years old and over, consent to participate in the study, were evaluated for TI-RADS III-V in ultrasound, and Bethesda V-VI in cytology, and whose



tumour size was up to 4 cm, were included in the study. Patients with ASA (American Society of Anesthesiologists) >3 or thyroid tumours other than of follicular origin as well as pregnant women were excluded from the study. Patients who met the inclusion criteria underwent a detailed thyroid ultrasound to assess whether laser ablation was feasible. If, after ultrasound evaluation, the patient was not suitable for laser ablation, ultrasound rejection criteria for laser ablation were established and the standard surgical treatment - thyroidectomy - was carried out. If laser ablation is safe for the surrounding structures, calcitonin was tested to rule out non-follicular cancers. After the normal results, under general anesthesia and under the control of the ultrasound, a core needle biopsy is taken, and laser ablation of the tumour node is performed at a wavelength of 1064 nm (power of 3 W). The standard surgery for thyroid tumour treatment - thyroidectomy - is then started. After the incision is made, neurostimulation of the nervus vagus is performed to ensure that the nerves have not been damaged during the laser ablation. Once the thyroid gland is removed, it is sent for histological examination.

#### Results

From February 2023, 10 patients have so far been enrolled in the study. 3 of them have undergone laser ablation and the remaining 7 were considered not suitable for laser ablation. The mean age of the patients undergoing laser ablation was 57.33 ( $\pm$ 19.60) years and the mean age of patients excluded from laser ablation due to ultrasound evidence of unsafety was 47.71 ( $\pm$ 16.00) years. The mean maximum thyroid nodule dimension in patients undergoing laser ablation was 18.93 mm ( $\pm$ 5.8) while for the other group with no laser ablation – 16.67 mm ( $\pm$ 5.91 mm). An 18 G diameter laser fiber was introduced into the node. Thyroid nodules were ablated according to the recommendations of the 2022 Expert Consensus Statement on the Use of Laser Ablation in the Treatment of Papillary Thyroid Microcarcinoma and the recommended parameters set by the laser manufacturers (Biolitec biomedical technology GmbH) at 3 W until the node seems coagulated echoscopically. There were no complications (intraoperative and postoperative) due to laser ablation. Histological examination of two thyroid glands (maximum node diameter – 22 and 24 mm) showed a zone of complete coagulation (carbonization) and thermal changes, which did not completely cover the entire area of the tumour tissue, and there was the tumour tissue that looked unchanged on histological staining. In the third patient (with a maximum nodal dimension of 10 mm), a zone of carbonisation was also observed and the hyperthermic lesions covered the entire tumour area.

#### Conclusions

We found that laser ablation is feasible in 30 percent of thyroid carcinoma patients in our experience. Of the patients, who underwent laser ablation, there remains the possibility of incomplete thermal effect on the tumour. To the best of our knowledge, this is the first study to evaluate the histological effect of laser ablation. Further studies are needed on the exact parameters, the coagulation technique, and the application of histological stains to assess the viability and possible reversibility of the cells in the hyperthermic zone.

#### Brief description of the abstract

Laser ablation was presented in the 2022 consensus as an alternative treatment for papillary thyroid microcarcinomas. In addition to laser ablation, our study continues to perform thyroidectomy and histological evaluation of laser ablation. Our initial findings suggest that histologically there remains an area of unclear tumour viability, which requires further study using histological stains.

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### **P-04 Parathyroid carcinoma: an analysis of 10 consecutive patients treated in the Hospital of LUHS Kauno Klinikos**

Track: Endocrine surgery

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- 2) *Virgilijus Krasauskas*, Lithuanian University of Health Sciences Hospital Kauno Klinikos, Lithuania
- 3) *Vy gintas Šlenfuktas*, Lithuanian University of Health Sciences Hospital Kauno Klinikos, Lithuania
- 4) *Valentinas Matulevičius*, Lithuanian University of Health Sciences, Lithuania
- 5) *Valdas Šarauskas*, Lithuanian University of Health Sciences Hospital Kauno Klinikos, Lithuania
- 6) *Ieva Vincerževskienė*, National Cancer Institute, Lithuania

#### Objective

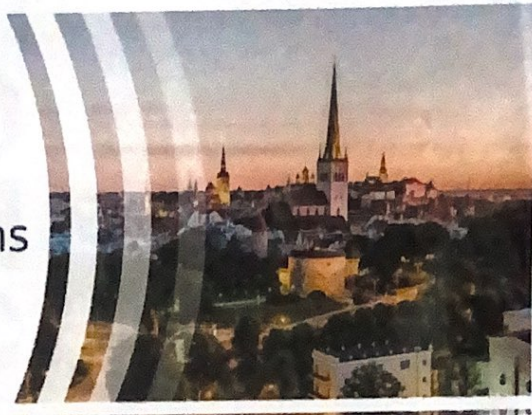
Parathyroid carcinoma (PC) is considered a rare malignancy which accounts for less than 1% of hyperparathyroidism cases in reported literature. In B. C. James study there were only 348 cases of PC reported in SEER database 2000-2012, which compose 0,36 (per 1 million) incidence rate. PC occurrence is equal in men and women, while benign parathyroid diseases incidence is higher in women with ratio 3-4:1. Diagnostic criteria were established in 1973 by A. Schantz and B. Castleman which include thick fibrous bands, mitotic activity, vascular and capsular invasion in pathomorphological tests. The variations and pathognomic features are debated as there have been reported large series of patients with metastatic tumours of which as many as 50% were initially misdiagnosed as benign tumours, therefore preoperative diagnosis and staging is often incorrect or not available. Imaging techniques such as sestamibi scintigraphy and neck ultrasound are only used in localizing the parathyroid tissue preoperatively and >3cm size mass may raise suspicion of PC as denoted in Cetani study, however these techniques are in no way diagnostic of PC. This lead to diagnostic markers application such as Ki-67, Cyclin D1, which are more specific to PC than parathyroid adenoma. The course of disease is indolent and most deaths occur due to untreated complications of hypercalcemia. Ten cases of PC were treated in our hospital during the period of 17 years. This review focuses on our experience with the diagnosis, treatment and survival of the patients. Our aim was to review the demographics, diagnostics, treatment and outcomes of the patients, who were surgically treated for parathyroid carcinoma in the Hospital of



2023

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P-03

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## Persiųsta: Notification of abstract acceptance - ESES Congress Rome 2024

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2024-02-26, Pr 12:43

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Dear Prof. Augustas Beiša,

on behalf of the ESES Executive Council, we are very pleased to inform you that your abstract ID 97 (Internet ID 114670) entitled

**LASER ABLATION APPLICABILITY IN TREATMENT OF THYROID CANCER: ONGOING TRIAL**

submitted for consideration for the **10<sup>th</sup> Biennial ESES Congress in Rome, 23 – 25 May 2024**, has been accepted for **E-POSTER** presentation.

We congratulate you and your co-workers for the excellent quality of your work that was very highly marked by independent ESES reviewers and selected among 318 submitted abstracts!

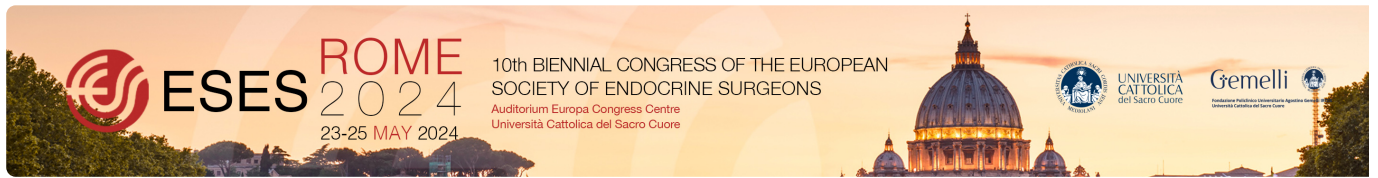
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# 10th Biennial Congress of the European Society of Endocrine Surgeons

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ID Abstract

97

Topic

Thyroid

Abstract Title

LASER ABLATION APPLICABILITY IN TREATMENT OF THYROID CANCER: ONGOING TRIAL

Background

Minimally invasive procedures such as laser ablation (LA) are gaining ground in modern surgery to reduce post-operative changes in quality of life. This encouraged the exploration of the applicability of LA in patients with papillary thyroid cancer (PTC), therefore, we aimed to evaluate the feasibility and histological effect of LA in patients with PTC.

Method

Patients with cytologically suspected or confirmed thyroid carcinoma - Bethesda grades V-VI - were included in the study. Before thyroidectomy, thyroid nodules were evaluated ultrasonographically for the suitability of safe and effective LA. Suitable patients underwent LA followed by thyroidectomy. Specimens with ablated tissue, residual tumor, and unaffected parenchyma were measured and evaluated using triphenyl tetrazolium chloride (TTC) solution, histologic (hematoxylin and eosin), and immunohistochemical methods (using NADPH oxidase 4). If patients were not eligible for LA, the reason was documented, and a thyroidectomy was performed.

Results

From 7th February till 1st December 2023, 16 patients have been enrolled in the study. 6 of them (37.5%) were eligible for LA. Macroscopic and microscopic examination of the lobes revealed an LA-induced central carbonization zone, alongside TTC-negative, NADPH4-negative coagulative change in the residual tumour. Unaffected thyroid tissue retained normal histology, TTC- and NADPH-positivity.

Conclusion

To our knowledge, this is the first study that demonstrates laser ablation-induced irreversible histochemical changes in papillary thyroid carcinomas. Ongoing trial will collect important data on LA feasibility, patient selection, and appropriate LA procedure parameters.

Status

Accepted

Session

P3 - Posters Thyroid

Presentation scheduled at

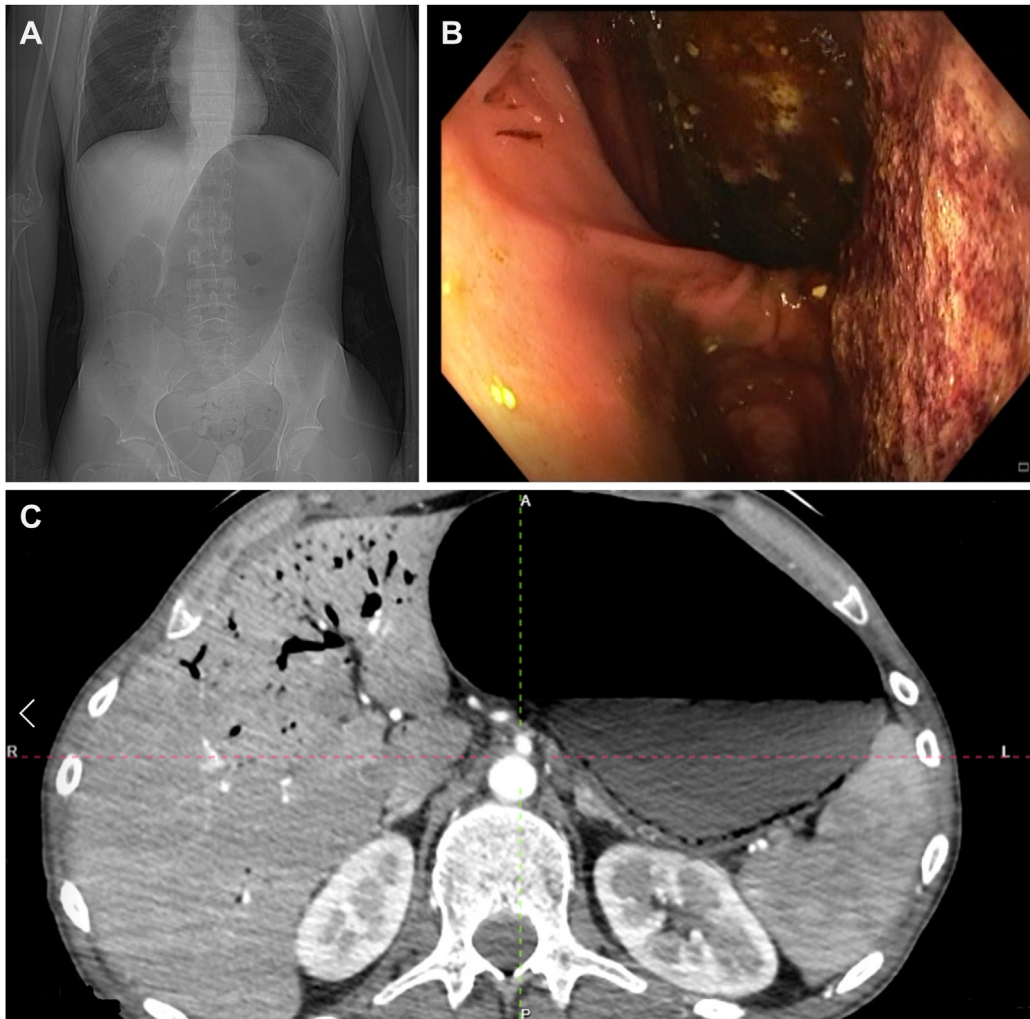


## 29-Year-Old Man With Acute Gastric Distention



Kristina Marcinkeviciute,<sup>1</sup> Tomas Poskus,<sup>1,2</sup> and Andrius Berukstis<sup>1,3</sup>

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**Question:** A 29-year-old man presented to the emergency department with acute abdominal distention, nausea, and vomiting. The patient had undergone 2 laminectomies and spinal cord decompression surgery due to subdural and subarachnoid hematoma after rupture of an arteriovenous malformation 2 months ago and he experienced tetraparesis and dysfunction of the pelvic organs since surgery. He had been diagnosed with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis and focal necrotizing and crescentic glomerulonephritis 10 years ago and for the last 5 years he was asymptomatic and did not undergo any treatment until the spinal cerebral incident.

On arrival at the emergency department, he complained of abdominal pain, distention, and vomiting episodes. During the clinical examination, the patient's abdomen was distended and nontender. No rebound tenderness was evident. Normal white blood cell count with elevated C-reactive protein of 128.7 mg/L (normal <5 mg/L) was evident. Antibiotics were immediately started due to high inflammatory markers and suspected bacterial infection. Abdominal ultrasound was

# ELECTRONIC *GASTRO* CURBSIDE CONSULT

uninformative due to a large amount of intraluminal gas in the bowel, but there was suspected volvulus of the colon. Abdominal X-ray detected an extremely dilated stomach without a clearly identifiable reason (Figure A). Portal venous gas shadow is evident in the liver, however, it was not reported on the original report. Nasogastric tube was inserted to remove the liquid from the stomach and an esophagogastroduodenoscopy (EGD) was performed. Dilated stomach with a dark-colored mucosa of the posterior wall was visible (Figure B). Abdominal computed tomography (CT) with angiography was performed and revealed significantly dilated stomach (320 x 149 x 95 mm), pneumatosis of the gastric wall, air in the portal system, and significant stenosis (90%) of the proximal part of the celiac trunk (Figure C).

What is the diagnosis?

See the *Gastroenterology* website ([www.gastrojournal.org](http://www.gastrojournal.org)) for more information on submitting to *Gastro Curbside Consult*.

#### Correspondence

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#### Acknowledgments

Kristina Marcinkeviciute, Tomas Poskus, and Andrius Berukstis contributed equally to this work.

#### Conflicts of interest

The authors disclose no conflicts.

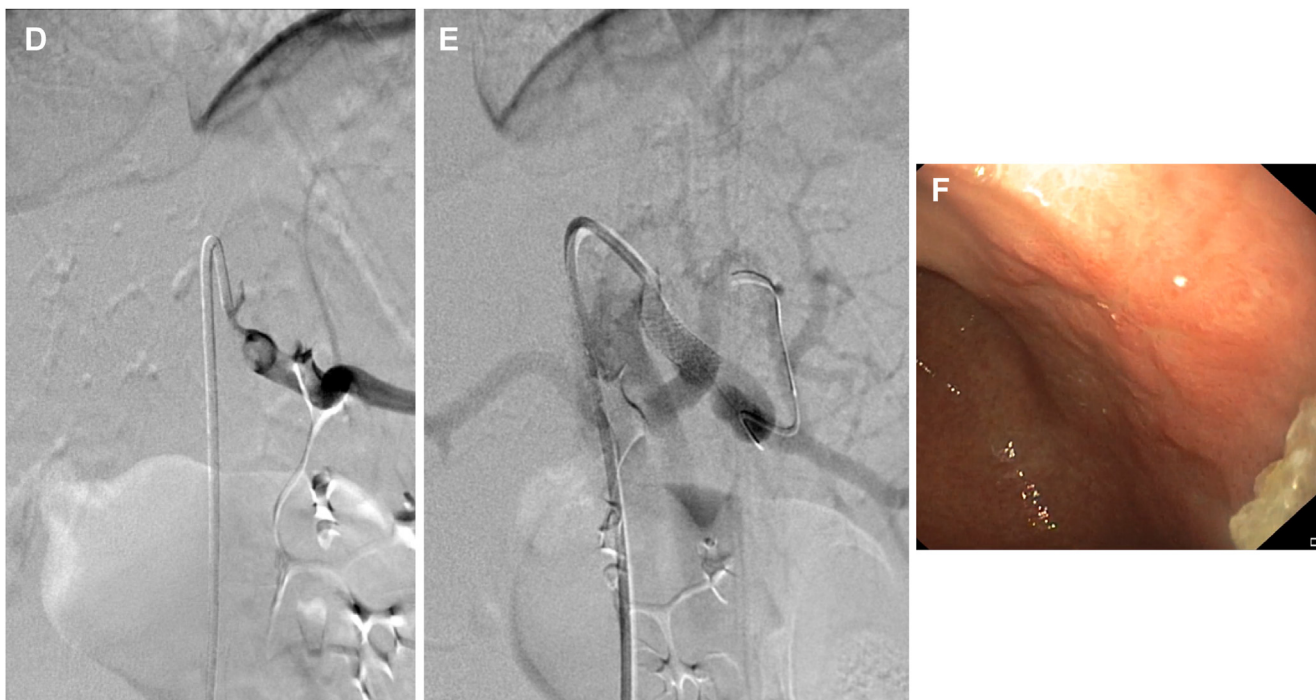
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<https://doi.org/10.1053/j.gastro.2022.09.017>

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Answer to: Image 2: Acute Gastric Ischemia



Abdominal X-ray findings were informative (showed a highly dilated stomach), but nonspecific. EGD suggested acute gastric ischemia due to the dark-colored mucosa of the posterior wall. Abdominal CT with angiography confirmed the diagnosis of gastric ischemia, pneumatosis of the gastric wall, and air in the portal venous system, but also revealed critical stenosis (90%) of the proximal part of the truncus coeliacus that was the reason for the gastric ischemia. Emergency angiography (Figure D) was performed with stenting of the truncus coeliacus (Figure E). After the procedure, antithrombotics were started and intravenous proton pump inhibitors were also administered. One week after stenting, repeated upper endoscopy showed superficial ulceration on the posterior wall of the stomach. After 12 months of follow-up, the patient had no stomach or abdominal symptoms and mucosal scar was visible on upper gastrointestinal endoscopy (Figure F).

Acute gastric ischemia is an extremely rare clinical condition due to rich collateral blood supply of the stomach.<sup>1</sup> Although mesenteric ischemia accounts for only 0.09%–0.2% of all acute surgical admissions worldwide, acute truncus coeliacus ischemia is even more rarely reported in the literature.<sup>2</sup> Predisposing factors, such as atherosclerosis, vasculitis, paraesophageal hernia, gastric volvulus, gastric dilation, disseminated intravascular coagulation, shock, and postoperative state, might increase the risk of gastric ischemia.<sup>3</sup> Unfortunately, our patient had a history of ANCA vasculitis that was most likely one of the causes of stenosis of the celiac trunk. The diagnosis of gastric ischemia should be considered for patients presenting with acute nonspecific symptoms: abdominal pain, distention, nausea, or vomiting. Although ultrasound is usually uninformative, for primary diagnosis, an abdominal x-ray may be chosen, where the dilated stomach is visible. EGD and endotracheal intubation to protect the airway during the EGD should be performed. Ischemic changes and their extent in the mucosa can be visualized on endoscopy. The most important diagnostic tool for gastric ischemia is CT angiography. It can identify the area of ischemic changes, possibly the cause (as in the presented case), and also the signs of perforation. If these are present, upper gastrointestinal endoscopy is contraindicated. The treatment of this disease includes immediate revascularization of the stomach, as in the presented case. Because the diagnosis and treatment were quick enough, full-thickness necrosis of the stomach was avoided. If the diagnosis is late and the stomach wall becomes necrotic, partial or total gastrectomy is required, depending on the extent of the necrosis.

Gastric ischemia has a poor prognosis, so thorough clinical examination, early diagnosis, and prompt treatment are mandatory in preventing fatal complications.

**Keywords:** Gastric Distention; Abdominal Pain; Gastric Ischemia.









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## Article

# Combined Femtosecond Laser Glass Microprocessing for Liver-on-Chip Device Fabrication

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**Abstract:** Nowadays, lab-on-chip (LOC) devices are attracting more and more attention since they show vast prospects for various biomedical applications. Usually, an LOC is a small device that serves a single laboratory function. LOCs show massive potential for organ-on-chip (OOC) device manufacturing since they could allow for research on the avoidance of various diseases or the avoidance of drug testing on animals or humans. However, this technology is still under development. The dominant technique for the fabrication of such devices is molding, which is very attractive and efficient for mass production, but has many drawbacks for prototyping. This article suggests a femtosecond laser microprocessing technique for the prototyping of an OOC-type device—a liver-on-chip. We demonstrate the production of liver-on-chip devices out of glass by using femtosecond laser-based selective laser etching (SLE) and laser welding techniques. The fabricated device was tested with HepG2(GS) liver cancer cells. During the test, HepG2(GS) cells proliferated in the chip, thus showing the potential of the suggested technique for further OOC development.

**Keywords:** selective laser etching; 3D laser microfabrication; laser welding; glass microfluidics; femtosecond laser microprocessing



**Citation:** Butkutė, A.; Jurkšas, T.; Baravykas, T.; Leber, B.; Merkininkaitė, G.; Žilėnaitė, R.; Čereška, D.; Gulla, A.; Kvietkauskas, M.; Marcinkevičiūtė, K.; et al. Combined Femtosecond Laser Glass Microprocessing for Liver-on-Chip Device Fabrication. *Materials* **2023**, *16*, 2174. <https://doi.org/10.3390/ma16062174>

Academic Editors: Tsung-Yuan Kuo and Hong-Chuong Tran

Received: 15 February 2023

Revised: 3 March 2023

Accepted: 7 March 2023

Published: 8 March 2023



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## 1. Introduction

Nowadays, a remarkable idea in medical treatment and diagnostics is that of lab-on-chip (LOC) devices, which allow the miniaturization of massive diagnostic tools and the reduction of testing on live organisms. The LOC technology has become more and more promising as an innovation in the research field because of such devices' functionality. Usually, a single chip is integrated with one or several laboratory functions, allowing laboratory processes to proceed quickly with high precision. In combination with the working principles of microfluidics, these devices show potential in health applications, medicine, and more. The designs and applications go in various directions—for example, injection-molded polymeric LOC for blood plasma separation [1], plastic LOC for herbicide residue monitoring in soil [2], and devices for the detection of various pathogens in food [3,4], for the detection of viruses [5,6], and for the detection of bacteria [7]. The applications of LOC devices do not end here; they could be used for research on various cells, such as research on the growth of fungal cultures [8] or on cancer and tumor cells [9–11]. LOC devices could also be used for tissue or organ research. These devices are usually called organ-on-chips [12] or organoids-on-chips (OOCs); as the name suggests, these are chips with an organ/organ tissue that is grown inside the chip and will later be used for various

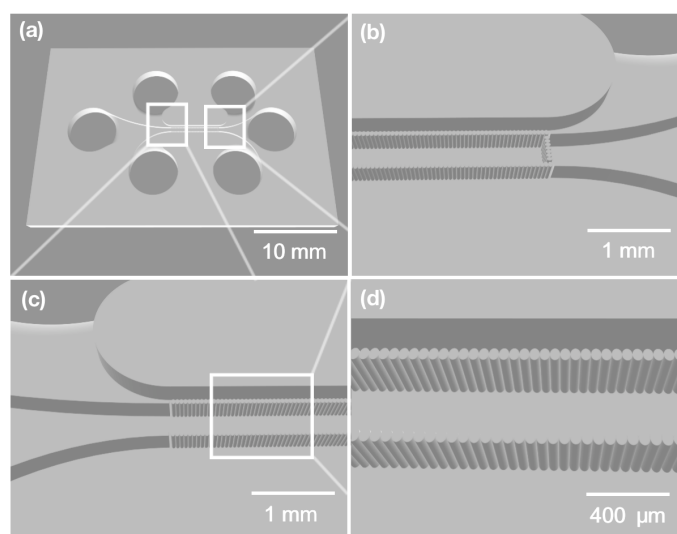
tests, such as tests on drugs [13,14], toxins [15], and others [16]. One example is a liver-on-chip device [17]. OOC devices are becoming more popular because of their versatility and advantages in comparison with usual testing methods. LOC devices are rapidly merging directions. However, this is still an open area for innovations—from new materials to innovative design research.

The dominant technology in the production of such devices is molding [18,19]. On one hand, molding is a very effective and cheap technique for mass production [20]. Molded chips can cost a few euros per piece. On the other hand, the price can increase by many times (even hundreds of times) for prototyping when new master structures are needed for any changes in the chip design. We propose an alternative solution based on ultrafast laser material processing in this work. Even though laser micromachining is quite an expensive process, with which the price of a chip could be in the range of tens to hundreds of euros, it is a good tool for the prototyping of complex devices. Femtosecond-pulse lasers are a powerful tool and bring a few significant advantages for material processing, such as high precision and high quality. In addition, this tool leads to entirely new microprocessing techniques based on nonlinear material–light interactions, which are impossible with other tools. One example is the multi-photon polymerization [21,22] technique, which enables the fabrication of hundreds of 3D structures with nanometer precision and resolution out of polymers. Furthermore, a femtosecond laser is an excellent tool for glass microprocessing. Due to nonlinear light–material interactions, glass can be modified directly in the volume without damaging its surface [23]. A few different modifications can be created inside a volume of glass: changes in the refractive index [24], nanogratings [25], or microvoids [26]. The type of modification induced depends on the radiation intensity used [24]. However, each type of modification can be used for the microprocessing of different materials. For instance, by inscribing a refractive index or nanogratings, refractive optical elements can be formed [27]. A combination of the inscription of nanogratings with subsequent selective laser etching (SLE) could be implemented [28,29]. Meanwhile, microvoid modifications were formed during laser ablation [30] to remove a material directly or during the laser welding process [31] to bond two materials together in their contact. Therefore, many different tasks could be accomplished with a single femtosecond laser source.

This study demonstrates a combination of a few different femtosecond glass microprocessing techniques for liver-on-chip device manufacturing. Here, we combine the selective laser etching and welding techniques to produce a liver-on-chip device. At the end, we provide the results of tests on the manufactured devices.

## 2. Materials and Methods

The main idea was to create an OOC prototype that is suitable for liver-on-chip testing by using femtosecond laser microprocessing methods. First of all, the concept of the device design was chosen. The central principle was to create a microfluidic system with three individual channels that were separated in the center with filters. The center channel needed to be filled with liver cells. Meanwhile, the side channels could be filled with other materials, such as drugs or different types of cells. The reactions between liver cells and the drug could be observed in the mentioned chip area. A similar design concept with pillar filters has already been published elsewhere [32]. However, the design of the microfluidic channels was significantly changed. The critical requirements in microfluidics are keeping channels as short as possible and avoiding microwells, dead-ends, or sharp forms in the channels. The microfluidic chip design that was created is shown in Figure 1. These adjustments make microfluidic systems more user friendly because the channels can be filled without sophisticated microfluidic pumps. In the described experiments, simple lab pipettes were used to manipulate substrates and fill the designed chip.

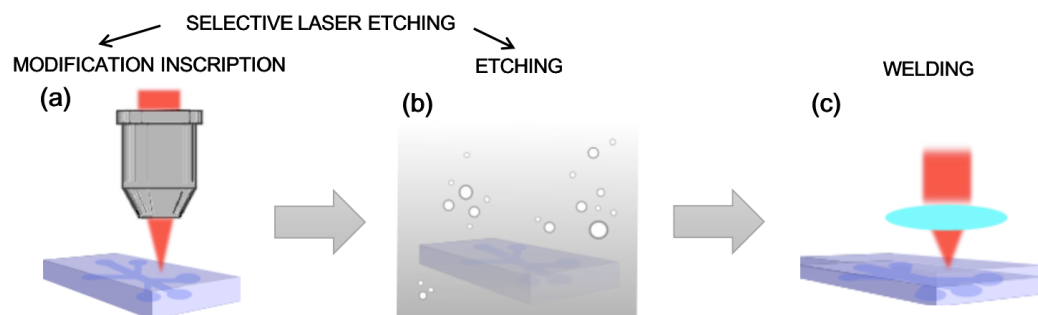


**Figure 1.** A picture of the liver-on-chip model that was created. (a) A full view of the chip model; three cylindrical holes serve as inlets for each channel, and three cylindrical holes are outlets for each of the three channels. All three channels meet in the center and are separated by a pillar-type filter. (b,c) An enlarged view of specific parts of the channel system. (d) Glass-type filters in the center of the chip.

For liver-on-chip fabrication, two different laser microprocessing methods were used. Plates with channel systems and integrated filters were fabricated with the SLE method. SLE is a technology that enables the production of 3D structures out of solid-state transparent materials [33,34]. The implementation of SLE consisted of several steps. First, laser-induced periodic modifications called nanogratings were formed in the volume of the material by using ultrashort pulses. Subsequently, a laser-modified material was etched out with aggressive etchants, such as hydrofluoric acid (HF) or potassium hydroxide (KOH) [35]. SLE was performed on amorphous UV-grade fused silica (UVFS) with a 1 mm thickness. The UVFS substrates were chosen for the fabrication of the channel system. Laser microfabrication was performed by using a Laser NanoFactory workstation (Femtika Ltd., Lithuania). The utilized workstation was equipped with a Yb:KGV femtosecond laser (Pharos, Light Conversion Ltd., Lithuania). For the SLE experiments, a fundamental wavelength of 1030 nm, a 700 fs pulse duration, and a frequency of 610 kHz laser radiation was used. The laser radiation was focused with  $20 \times 0.45$  NA Nikon focusing objective equipped with automated aberration correction (add-on device from Femtika Ltd., Vilnius, Lithuania). Within specific radiation exposition conditions, modifications in porous materials called nanogratings could be inscribed inside the volume of the glass [25]. Subsequently, after inscribing particular material modifications, the sample was etched in a potassium hydroxide (KOH, Eurochemicals, Lithuania) solution at a 6 mol/L concentration with distilled water at a temperature of 90 °C. The etching protocols were optimized for the fastest etching procedure. This optimization has already been published elsewhere [36].

Since we needed an encapsulated microfluidic channel system, the channels formed on the plates had to be sealed. Another femtosecond-laser-radiation-based technique—laser welding [37,38]—was used for that. Only the contact between two plates could be affected without damaging the surface by using high-intensity radiation due to nonlinear light–material interactions. With high power, the material in the contact could be melted, and a firm connection was formed in the mentioned samples. The laser welding part was carried out with the same Laser NanoFactory workstation. The laser welding experiments are conducted with the same 1030 nm wavelength, a pulse duration of approximately 200 fs, and a 610 kHz pulse repetition rate. The laser radiation was focused with a 0.5 NA aspherical lens. After the etching and before the welding, the samples were washed in a piranha solution (4:1 *v/v* of sulfuric acid (95–98%, Sigma-Aldrich, Darmstadt, Germany) and

hydrogen peroxide (50%, Sigma-Aldrich, Darmstadt, Germany), respectively). Afterward, the samples were rinsed in distilled water and isopropanol. The basic scheme of the fabrication of the chips is shown in Figure 2.



**Figure 2.** A basic scheme of the laser processing of the lab-on-chip devices. (a) Inscription of nanogratings on the glass plate by focusing light with a microscopic objective. (b) Subsequent etching of the laser-processed sample. (a,b) Presentation of the SLE technique. (c) The laser welding process used to seal the channel system with an additional glass plate.

The manufactured liver-on-chip prototypes were rinsed with sterilized aqua dest, submerged in 70% ethanol solvent for initial disinfection, and UV irradiated for 20 min for further sterilization. The chips were coated with poly-L-lysine polymers to promote cell adhesion. The coating was performed by filling the chamber with 10  $\mu$ L of poly-L-lysine solution (Sigma Aldrich, Vienna, Austria) through a seeding channel, followed by an incubation period at 37  $^{\circ}$ C until they had completely dried. These prepared liver-on-chip systems were stored in standard sterile conditions until use.

The human liver HCC cell line HepG2(GS) (originating from ATCC, Rockville, MD, USA) was used for biocompatibility testing. These cells were cultivated under standard conditions (37  $^{\circ}$ C, 5% CO<sub>2</sub> in a humidified atmosphere) in MEM media (Gibco, Thermo Fisher Scientific, Vienna, Austria) supplemented with 10% fetal bovine serum (GE Healthcare Life Sciences, UT, USA) and 1% penicillin/streptomycin (Sigma Aldrich, Vienna, Austria). The media were renewed every other day, and cells were passaged once they grew to 80–90% confluence. The chambers of the liver-on-a-chip systems were filled with 10  $\mu$ L of a cell suspension to reach  $2 \times 10^4$  HepG2(GS) cells/cm<sup>2</sup> through the seeding channels. The chips were submerged in culture media in a Petri dish and placed in a cell incubator under standard conditions (37  $^{\circ}$ C, 5% CO<sub>2</sub> in the humidified atmosphere) overnight to avoid evaporation. Then, cell adherence and growth were determined through daily microscopic examination. The media were renewed every other day in a standard manner. Finally, the Trypan Blue exclusion test was conducted to further confirm cell viability. The total testing time frame for a single sample was nine days. This experiment was repeated three times in separate pieces. Every sample was used for a single experiment and then disposed of as waste due to the biological exhaustion of the sample.

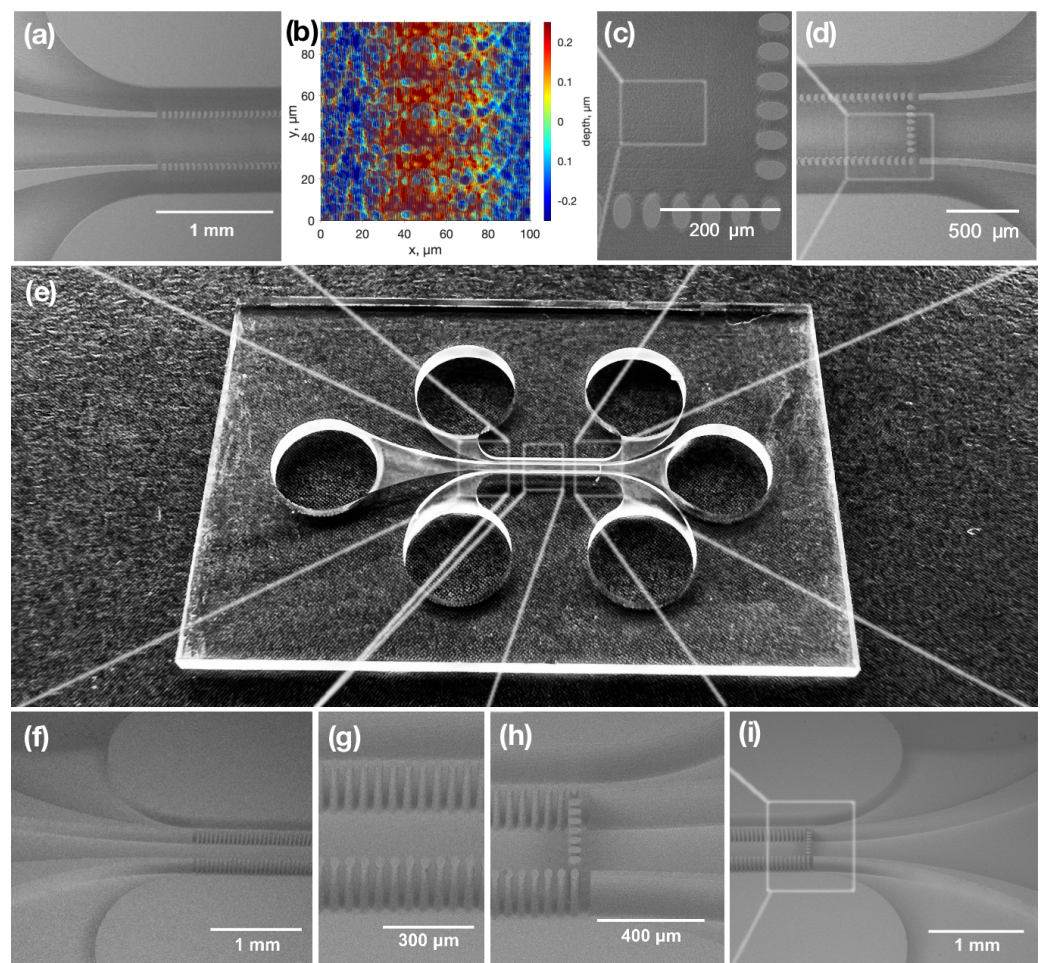
### 3. Results and Discussion

#### 3.1. Fabrication of the Microfluidic Chips

We began the research by producing microfluidic chips with integrated filters on a glass substrate. A picture of a fabricated chip and SEM pictures of its particular parts are shown in Figure 3. In general, the filter was a row of elliptical glass pillars. The dimensions of every pillar were a width of 36  $\mu$ m and a length of 55  $\mu$ m. The spacing between each pillar was 14  $\mu$ m, corresponding to the filter's pores. The height of the fabricated pillars was 200  $\mu$ m, which was identical to the depth of the microfluidic channel. The filters were integrated into a channel that was 5 mm long and 0.9 mm wide. In the mentioned area, two rows of pillars divided that zone into three distinguished channels; the side channels were 200  $\mu$ m wide, and the central one was 400  $\mu$ m wide.



Visually, smooth features and a high channel aspect ratio were obtained. However, not only modified but also unmodified material was etched during the etching process. Thus, this led to widened channels and features. The mentioned effect created a critical limitation of the aspect ratio, which is especially important in microfilter fabrication. Since the cells were micro-scale objects, the precision of the integrated filter was essential. In the model, the gap between pillars shown in Figure 3c,g was a single-line inscription, which was a minimal laser modification between pillars. However, after the etching, the gap between pillars tended to increase up to 14  $\mu\text{m}$ , which limited the accuracy and minimal features of the filter. In LOC applications, the surface quality of the channel is also critical. This feature affects liquid flow. The higher roughness of the surface, the more friction it creates. Thus, the channels become difficult to fill due to the higher surface roughness. The surface quality of the processed channels was evaluated with an optical profilometer. The surface roughness of the etched channels was around 250 nm root mean square (RMS). The surface topology of the channel is shown in Figure 3b.

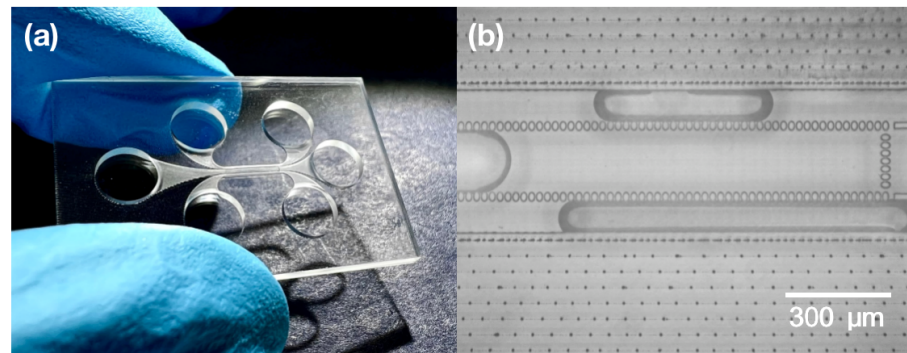


**Figure 3.** Pictures of the produced liver-on-chip device. (e) Optical picture of a full device. (a,c,d) SEM images of the tops of the specified chip parts. (f–i) SEM images of specified chip parts at 45°. (b) Surface topology of the channel surface.

### 3.2. Welding of the Microfluidic Chips

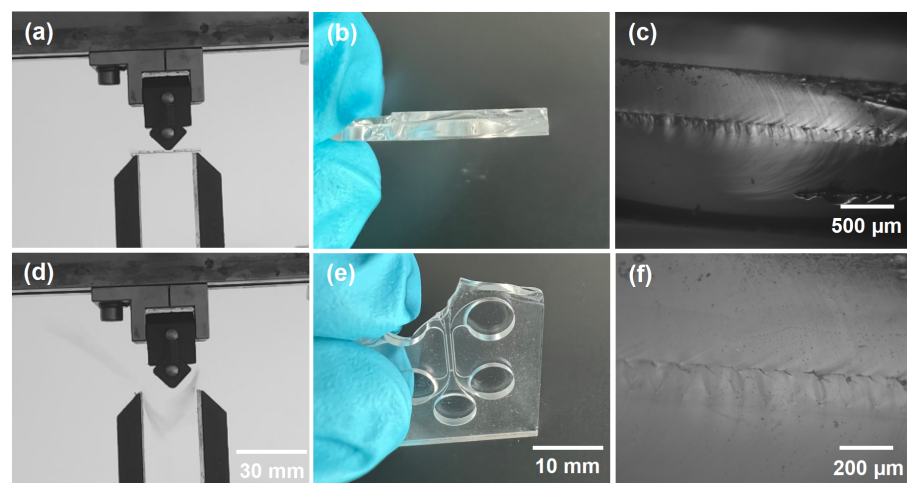
The chips were sealed through laser welding. Optical contact was required to create firm contact between plates. That meant that the gap between two surfaces should be a few times smaller than the wavelength used, which was 1030 nm. To achieve that, the high cleanness and surface quality of the samples was needed. Thus, the samples were washed in piranha solution to remove all organic remains from the chip. Before welding, the chip was rinsed in isopropanol and distilled water. Two glass plates were put on each other

when the chip was still wet. Isopropanol is a liquid that forms a low contact angle with glass [36], which means that it wets surfaces. Thus, due to the wet contact with isopropanol, the two plates tended to have a smaller gap between each other, which enhanced the welding quality. The two plates were welded in contact everywhere around the channel system without damaging or affecting the channels or the filters themselves. Welding seams were made within a spacing of 100  $\mu\text{m}$ . An image of the welding seams around the microfluidic channels is provided in Figure 4b. An optical picture of the produced chip is shown in Figure 4a.



**Figure 4.** (a) Picture of a final liver-on-chip device. (b) Optical picture of the produced microfluidic chip part where a channel with a filter and welding seams can be observed.

It was already demonstrated that the welding strength could be close to the mechanical strength of the bulk material [38]. However, we performed an additional experiment to test the welding quality. The main idea was to affect the chip with a particular force and test what forces led to the breaking of the chip. This experiment is shown in Figure 5a,d. The force was gradually increased, and the chip broke when it was affected by a 9.3 N force. A broken chip after the test is presented in Figure 5b,e. After the sample was broken, the chip was destroyed. Nonetheless, in most places, the welding seam still held the two glass plates together. Pictures were taken of the welding seam from the side of the broken chip Figure 5c,f. The welding seam seemed to have small periodic cracks; however, the material in between seemed to be completely fused between the two plates. The provided material contributed to the statement that the strength of the welding seam was comparable to the strength of the bulk material. The welding seam was not the weakest part of the chip. The chip tended to break through the channels, which were the most fragile parts of the chip.

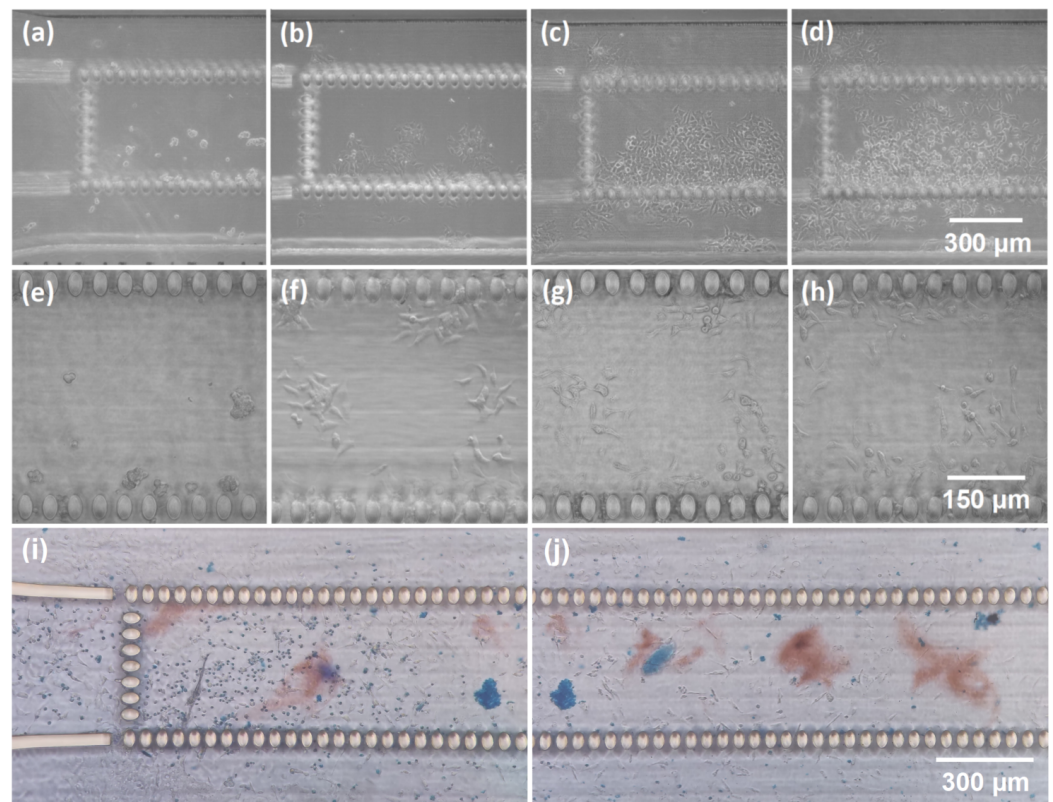


**Figure 5.** (a,d) Mechanical resistance test on the chip. (b,e) Photos of the broken chip after the mechanical resistance test. (c,f) Optical pictures of the broken structure's welding seam from the side of the sample.



### 3.3. Testing of the Liver-on-Chip's Functionality

The prototype device's functionality was tested with liver cells. A homogeneous film of poly-L-lysine was formed on the surface of the liver-on-chip systems. Uncoated chips were also tested; however, HepG2(GS) did not adhere due to the smooth chips' surface, while cells attached well on the coated surfaces. A total of 24 h after seeding, HepG2(GS) cells started to grow in a monolayer. The number of spheroids and size were consistent with the starting cell density. During the media change, the cell monolayers remained adherent to the surface and continuously grew. After 96 h of culture, the HepG2(GS) cells created large irregular spheroids. After 7 days of culture, the growth of spheroids led to the formation of large clusters of spheroids in the whole liver-on-chip system. A picture of the mentioned test is shown in Figure 6. From day 7, the cell viability decreased, as seen from the roundish shape of some of the cells. After 9 days, most of the cells had died according to the Trypan Blue test; this can be seen in Figure 6*i,j*. In general, the Trypan Blue exclusion test showed that the adhesive cells had good viability for 7 days of the experimental period.



**Figure 6.** Optical pictures of the fabricated microfluidic channels seeded with HepG2(GS) liver cancer cells (a): (e) right after the seeding, (b,f) after 24 h, (c,g) after 96 h, (d,h) after 7 days, (i,j) after 9 days with Trypan Blue.

### 3.4. Future Prospects

The results show that femtosecond laser glass microfabrication is suitable for the development of liver-on-chip devices. However, there is still space for manufacturing improvements and more flexible design implementations. One of the observed challenges was the filter's accuracy and the minimum pore size. For example, the accuracy of SLE-made features depends on the etching rate between the modified and unmodified material. With the currently used chip design and etching protocol, the minimum spacing between pillars is 14  $\mu\text{m}$ . Therefore, during the tests, it was noticed that a fraction of cells could pass through the filter and appear in other channels. Thus, the mentioned spacing between the pillars must be reduced to keep all of the cells inside the center channels. Therefore, the accuracy and sharpness of the structural etching rate of the modified material can



be increased. This can be achieved in a few ways, such as by optimizing the etching process, the etching solution [36], and the laser parameters [39], or by introducing a specific femtosecond burst regime [40]. Such improvements can create the possibility of tuning the filter size more accurately. Moreover, the surface quality of the fabricated chips can be increased by applying additional post-processing, such as heat treatment [41,42] or CO<sub>2</sub> laser annealing [43]. Such enhancements should decrease the friction between the surface of the channels and substances inserted in the chip, making it easier to fill the chip and test its functionality.

#### 4. Conclusions

Here, we demonstrated a flexible method for microfluidic prototyping. A microprocessing tool with a single femtosecond laser source was used to produce microfluidic channel systems with integrated glass pillar filters. The channels were hermetically sealed by welding a glass plate on top of the channels with the same femtosecond processing tool. In this way, the whole liver-on-chip device was manufactured with a single workstation. Afterward, the produced chips were tested as liver-on-chip devices by filling the central channel with HepG2(GS) liver cancer cells. The cells tended not to adhere to uncoated glass surfaces. However, the cells aggregated on channels coated with a homogeneous film of poly-L-lysine, making it possible to test other cells' reactions to various stimuli introduced to the chip. These experiments show that femtosecond glass microprocessing is a potential and attractive technique for developing liver-on-chip devices. Here, we showed a potential platform for HepG2(GS) liver cancer cell testing; however, some improvements to these technologies still need to be made.

**Author Contributions:** Conceptualization, A.B., B.L., A.G., P.S. and K.S.; Methodology, A.B., T.B., B.L. and P.S.; Software, T.B.; Validation, B.L.; Formal analysis, B.L.; Investigation, A.B., T.J., T.B., B.L., G.M. and R.Ž.; Data curation, T.J., T.B. and B.L.; Writing—original draft, A.B., D.Č. and M.K.; Writing—review & editing, G.M., R.Ž., D.Č., A.G., M.K., K.M., P.S. and K.S.; Visualization, A.B., T.J., B.L. and M.K.; Supervision, A.B. and P.S.; Project administration, K.S.; Funding acquisition, K.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the European Commission's program "EUREKA", Nr.01.2.2-MITA-K-702-10-0006.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data is contained within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# Short- and long-term outcome differences between patients undergoing left and right colon cancer surgery: cohort study

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Accepted: 27 March 2024  
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## Abstract

**Purpose** Since the literature currently provides controversial data on the postoperative outcomes following right and left hemicolectomies, we carried out this study to examine the short- and long-term treatment outcomes.

**Methods** This study included consecutive patients who underwent right or left-sided colonic resections from year 2014 to 2018 and then they were followed up. The short-term outcomes such as postoperative morbidity and mortality according to Clavien-Dindo score, duration of hospital stay, and 90-day readmission rate were evaluated as well as long-term outcomes of overall survival and disease-free survival. Multivariable Cox regression analysis was performed of overall and progression-free survival.

**Results** In total, 1107 patients with colon tumors were included in the study, 525 patients with right-sided tumors (RCC) and 582 cases with tumors in the left part of the colon (LCC). RCC group patients were older ( $P < 0.001$ ), with a higher ASA score ( $P < 0.001$ ), and with more cardiovascular comorbidities ( $P < 0.001$ ). No differences were observed between groups in terms of postoperative outcomes such as morbidity and mortality, except 90-day readmission which was more frequent in the RCC group. Upon histopathological analysis, the RCC group's patients had more removed lymph nodes ( $29 \pm 14$  vs  $20 \pm 11$ ,  $P = 0.001$ ) and more locally progressed (pT3-4) tumors (85.4% versus 73.4%,  $P = 0.001$ ). Significantly greater 5-year overall survival and disease-free survival ( $P = 0.001$ ) were observed for patients in the LCC group, according to univariate Kaplan-Meier analysis.

**Conclusions** Patients with right-sided colon cancer were older and had more advanced disease. Short-term surgical outcomes were similar, but patients in the LCC group resulted in better long-term outcomes.

**Keywords** Colon cancer · Right colectomy · Left colectomy · Complications · Anastomotic leak

## Introduction

Colorectal cancer (CRC) stands as the world's 3rd most prevalent cancer and the 4th leading cause of cancer-related deaths [1]. The conventional approach combines right-sided

and left-sided colorectal cancer for evaluating treatment outcomes [2, 3]. Considering the colon's development from the midgut and hindgut [4], it exhibits variations in embryonic origin concerning vascular and nerve supply, microbial load, and primary physiological functions of the left and right colons. Consequently, the location of the tumor may be important in influencing pathogenesis, development, and overall outcomes [5, 6].

The surgical procedures for right and left hemicolectomies differ in technique and complexity, potentially leading to different complication rates. Although right hemicolectomy was considered to be a simpler procedure because of the omission of colocolic or colorectal anastomosis and better postoperative results than left hemicolectomy [7–9], current literature presents diverse data on short- and long-term outcomes. Some studies suggest that patients after left

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colectomy face more postoperative complications, including increased surgical site infections, a higher incidence of ureteral injuries, and a greater conversion rate to open surgery, along with an extended hospital stay [10], especially for elderly patients due to anastomotic leak that also leads to higher mortality risk [11]. Conversely, other reports argue that complications are more frequent in patients undergoing right colectomy [12]. Results from the American College of Surgeons National Surgical Quality Improvement Program database show that mortality and major complication rates were similar between both groups [8].

Given the conflicting data in today's literature regarding postoperative outcomes in right and left hemicolectomies, we conducted this study to compare short- and long-term treatment results.

## Methods

### Ethics

Vilnius Regional Ethics Committee approved the study (No. 2019/3-1116-608, 2019-03-20) before it was conducted. A waiver for informed consent was given with respect to the retrospective nature of the study. All study-related procedures were performed following the Declaration of Helsinki of 1975, as revised in 1983.

### Patients, diagnostic pathway, surgery, and follow-up

The study was carried out at two major colorectal cancer treatment centers in Lithuania: the National Cancer Institute and Vilnius University Hospital Santaros Klinikos. All consecutive patients who underwent surgical treatment for colon cancer from January 2014 to December 2018 were screened for inclusion in the study. Patients with multiple colon tumors and patients who underwent surgery without primary anastomosis were excluded. The study included all patients who did not meet the exclusion criteria.

The standardized diagnostic pathway for colon cancer patients involved colonoscopy and biopsy, followed by chest, abdominal, and pelvic computed tomography (CT). Once the diagnosis of colon cancer was confirmed, and staging was completed, all patients underwent thorough discussion in multidisciplinary team meetings. For patients without distant metastases, radical surgery was typically scheduled. The decision to proceed with initial surgery or surgery after neoadjuvant chemotherapy in cases of metastatic disease was personalized based on individual considerations. After surgery, all patients were allocated for medical-oncologist consultation, and chemotherapy was administered based on individual case.

The type of surgery depended on tumor location and typically, tumors located on the right colon, hepatic flexure, or middle part of the transverse colon were treated with right colectomy, while tumors on the left-side colon, splenic flexure, and sigmoid colon were resected by left colectomy or sigmoid resection [13], although, the exact extent of surgery and the approach (open or laparoscopic) were selected by a surgeon. The standard follow-up protocol consisted of a carcinoembryonic antigen (CEA) blood marker and computed tomography (CT) scan every 3 months for the first 2 years, then biannually and annually until 5 years after surgery or patient's death. A colonoscopy was performed 1 year after surgery.

### Study outcomes

For comparison, patients were grouped into right colon cancer (RCC) and left colon cancer (LCC) groups based on tumor localization as mentioned above. The short-term study outcomes included: postoperative morbidity according to Clavien-Dindo score [14] and mortality, length of stay, and 90-day readmission rate. Long-term outcomes included overall survival (OS) and disease-free (DFS) survival. OS was defined as the time between diagnosis of colon cancer and death. DFS was defined as the time from diagnosis to the recurrence of disease.

### Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 25.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean  $\pm$  standard deviation (SD) and were compared across groups using independent samples *t*-test. Categorical variables are shown as proportions and compared using the  $\chi^2$  or Fisher exact tests, as appropriate. OS and DFS rates were analyzed by the Kaplan-Meier method and were compared between the study groups by the log-rank test. Multivariable Cox proportional hazard regression analysis was used to identify the factors impacting long-term outcomes. Hazards ratios (HRs) were presented with 95% confidence intervals (CI). In all statistical analyses, two-tailed tests were used and a *P*-value of  $< 0.05$  was considered to be significant.

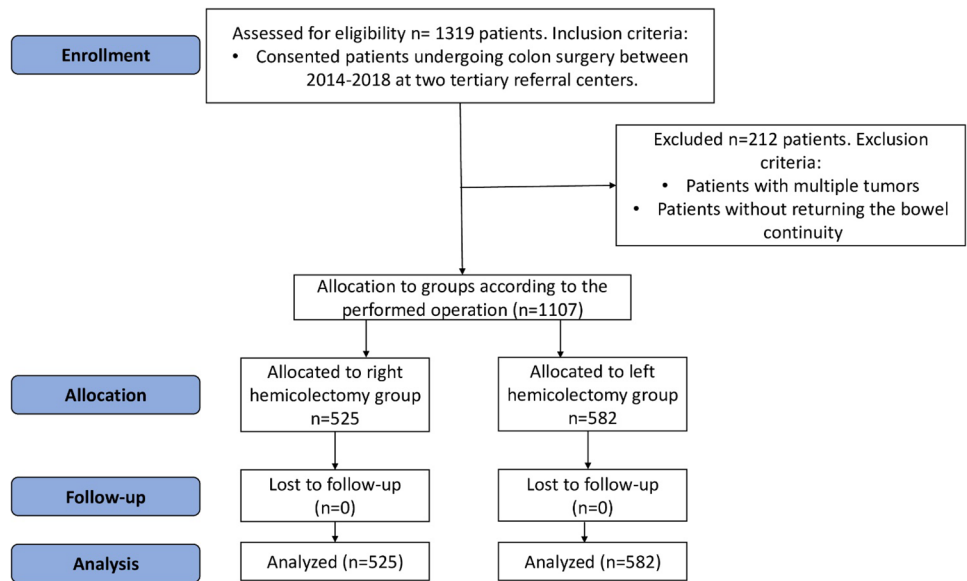
## Results

### Baseline characteristics

In total, 525 (47.4%) patients were included in the RCC group and 582 (52.6%) patients in the LCC group (Fig. 1).



**Fig. 1** A flow chart of included and excluded patients



The baseline characteristics of the groups are shown in Table 1. Patients in the RCC group were slightly older, had higher ASA scores and a higher proportion of these patients had cardiovascular comorbidities.

**Table 1** Baseline characteristics of patients in RCC and LCC groups

	RCC (n = 525)	LCC (n = 582)	P value
Age (years), mean ± SD	69 ± 11	66 ± 10	0.001
Sex, n (%)			0.001
Male	219 (41.7%)	307 (52.7%)	
Female	306 (58.3%)	275 (47.3%)	
American Society of Anesthesiologists score, n (%)			0.001
ASA 1-2	232 (44.2%)	378 (64.9%)	
ASA 3-4	293 (55.8%)	204 (35.1%)	
Comorbidities, n (%)			
Cardiovascular	271 (51.6%)	154 (26.5%)	0.001
History of stroke	16 (3.0%)	18 (3.1%)	0.999
Chronic renal failure	11 (2.1%)	12 (2.1%)	0.999
Diabetes	71 (13.5%)	70 (12.0%)	0.471
Stage of disease, n (%)			0.001
I	66 (12.6%)	128 (22.0%)	
II	193 (36.8%)	195 (33.5%)	
III	193 (36.8%)	192 (33.0%)	
IV	73 (13.9%)	67 (11.5%)	
Tumor localization, n (%)			N/A
Caecum	131 (25.0%)		
Ascending colon	264 (50.3%)		
Hepatic flexure	67 (12.8%)		
Proximal transversum	63 (12.0%)		
Distal transversum and splenic flexure		57 (9.8%)	
Descending colon		71 (12.2%)	
Sigmoid		326 (56.0%)	
Regtosigmoid junction		128 (22.0%)	

ASA American Society of Anesthesiologists score, N/A not applicable

### Surgical outcomes

Surgical outcomes and histology are shown in Table 2. A higher proportion of patients in the LCC group received minimally invasive surgery. Postoperative morbidity (24.7% vs 27.1%,  $P=0.366$ ) and mortality (2.1% vs 1.9,  $P=0.807$ ) rates between RCC and LCC groups were similar. Ninety-day readmission rate was higher in the RCC group (6.3% vs 2.1%,  $P=0.001$ ). Eleven patients in the right hemicolectomy group had an anastomotic leak, 1 was treated conservatively, and 10 were reoperated, while 41 patients in the left hemicolectomy group had an anastomotic leak, 11 were reoperated, 1 was drained, 1 was closed with an Ovesco staple, and 28 were treated conservatively. Histological examination showed that patients in the RCC group had a higher number of retrieved lymph nodes ( $29 \pm 14$  vs  $20 \pm 11$ ,  $P=0.001$ ) and more locally advanced (pT3-4) tumors (85.4% vs 73.4,  $P=0.001$ ).

### Long-term outcomes

The mean follow-up time was  $43 \pm 22$  months. Univariate Kaplan-Meier analysis showed a significantly higher 5-year OS (61.7% vs 74.1%;  $P=0.001$ ) and DFS (59.4% vs 70.4%;  $P=0.001$ ) for the patients in LCC group (Fig. 2). Although, multivariable Cox regression analysis demonstrated no evidence that the risk of death or disease progression was higher in RCC after adjustment for age, stage of the disease, and ASA score (Table 3).

### Discussion

This study examined both short- and long-term outcomes in patients with right and left colon cancer. The findings revealed that individuals with tumors on the right side tended

**Table 2** Surgery and postoperative outcomes of patients in RCC and LCC groups

	RCC ( <i>n</i> = 525)	LCC ( <i>n</i> = 582)	<i>P</i> value
Type of surgery, <i>n</i> (%)			N/A
Right colectomy	483 (92.0%)	1 (0.2%)	
Transversum resection	26 (5.0%)	2 (0.3%)	
Left colectomy	3 <sup>a</sup> (0.6%)	174 (29.9%)	
Sigmoidectomy/high anterior resection	0 (0%)	401 (68.9%)	
Total colectomy	11 (2.1%)	2 (0.3%)	
Segmental resection	2 (0.4%)	2 (0.3%)	
Length of surgery (minutes), mean ± SD	144 ± 51	139 ± 55	0.173
Surgical approach, <i>n</i> (%)			0.001
Open	437 (83.2%)	299 (51.4%)	
Minimally invasive	88 (16.8%)	283 (48.6%)	
Conversion rate, <i>n</i> (%)	9 (1.7%)	16 (2.7%)	0.247
Blood loss (ml), mean ± SD	130 ± 130	89 ± 137	0.377
Length of specimen (cm), mean ± SD	33 ± 14	21 ± 11	0.001
Retrieved lymph nodes number, mean ± SD	29 ± 14	20 ± 11	0.001
Pathological tumor stage, <i>n</i> (%)			0.001
pT1/2	77 (14.6%)	155 (26.6%)	
pT3/4	448 (85.4%)	427 (73.4%)	
Pathological nodal stage, <i>n</i> (%)			0.031
pN0	272 (51.8%)	339 (58.2%)	
pN+	253 (48.2%)	243 (41.8%)	
Radicality of surgery			0.942
R0	524 (99.8%)	581 (99.8%)	
R1-2	1 (0.2%)	1 (0.2%)	
Patients with postoperative complications, <i>n</i> (%)	130 (24.7%)	158 (27.1%)	0.366
Clavien-Dindo complications score			0.877
CD1/2	77 (14.7%)	95 (16.3%)	
CD ≥ 3	53 (8.0%)	63 (8.9%)	
90-days readmission rate, <i>n</i> (%)	33 (6.3%)	12 (2.1%)	0.001
Postoperative mortality, <i>n</i> (%)	11 (2.1%)	11 (1.9%)	0.807

N/A not applicable, CD Clavien-Dindo, pT pathological tumor stage, pN pathological nodal status

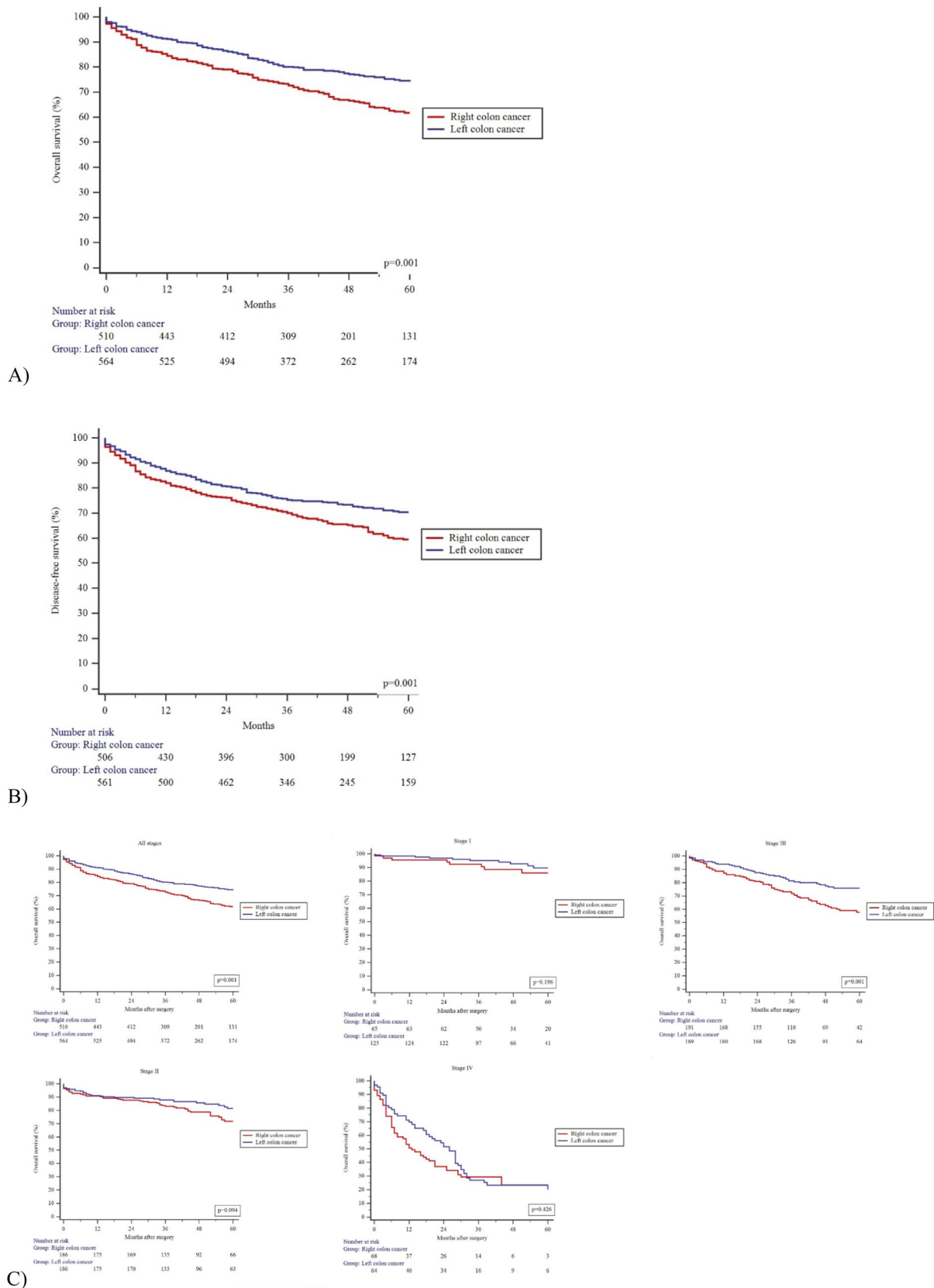
<sup>a</sup>The tumor was in the middle of the transverse colon

to be older and had more comorbidities. While there were no significant differences in short-term surgical outcomes, postoperative morbidity, and mortality between the two groups, a higher percentage of patients with right colon cancer experienced readmissions within 90 days postoperatively. Univariate survival analysis indicated a compromised survival rate among those with right colon cancer. This difference was attenuated after adjusting for patient age, disease stage, and physical status as represented by the ASA score.

A tendency toward higher age, greater comorbidities, higher ASA score (3/4) as well as more advanced tumors (T3/4), and higher rates of readmissions in our study was observed in the RCC group. Predominantly, minimally invasive surgery in LCC has not led to significantly lower morbidity rates compared to the more frequent open approach in RCC with additionally older and sicker patients. At the time of the study, laparoscopic operations were just entering

full clinical practice in these centers. This suggests that the surgeons might still be gaining proficiency and experience with minimally invasive techniques, leading to comparable morbidity rates between the two approaches. It was noticed in the literature that the age of operated patients and the location of the tumor are closely linked. The older the patient is, the more proximal to the ileocecal valve the tumor is [8, 12, 13, 15–20]. Patients were predominantly older in the RCC group most likely due to a delay in the detection of right-sided colon cancer. Cancer on the right side of the colon might present with more modest symptoms than cancer on the left side, which is frequently associated with anemia and weight loss, while left-sided colon cancer tends to cause partial bowel obstruction leading to constipation, narrowed stool, diarrhea, abdominal pains, tenesmus, bloating, and visible rectal bleeding, or complete bowel obstruction needing emergency treatment [13, 21]. Moreover, in some





**Fig. 2** Kaplan-Meier curves. **A** Overall survival (OS). **B** Disease-free survival (DFS). **C** Subgroups according to each stage of colon cancer in OS. **D** Subgroups according to each stage of colon cancer in DFS

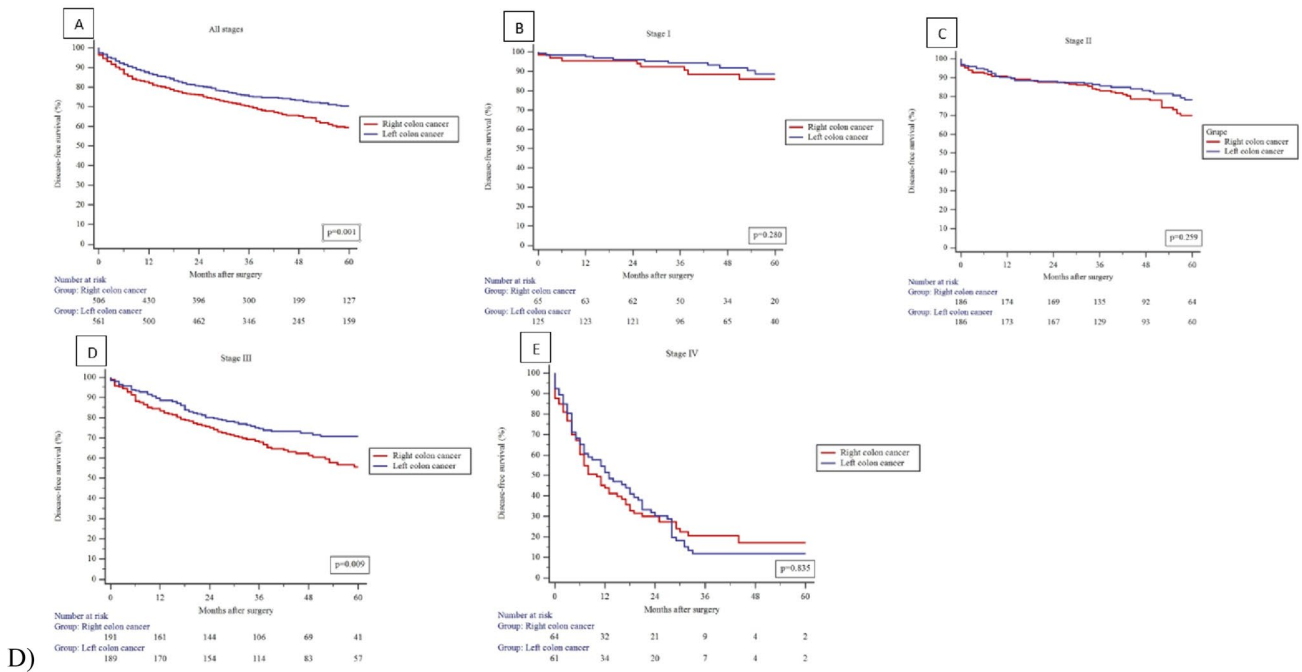


Fig. 2 (continued)

countries younger patients undergo screening sigmoidoscopy (UK guidelines), and more tumors in the left colon side are detected earlier than symptoms start [22]. Despite that the time from cancer onset to clinical symptoms is considered to be similar for both sides of the colon — between 4.5 and 5.8 years [23], our study shows that RCC group patients present with more advanced tumors (T3-4). As a result, it can lead to more difficult surgery, worse outcomes, and more frequent re-hospitalization due to complications. Study shows that advanced cancer is a significant risk factor for anastomotic leakage, and therefore to poorer outcomes [24]. On the other hand, there is evidence in the literature that tumors on the right and left sides of the colon have completely different molecular and histological characteristics.

Mutations in the DNA mismatch repair pathway are often found in RCC tumors, which are more sensitive to immunotherapy and less sensitive to chemotherapy, whereas LCC tumors are usually characterized by molecular mutations in the chromosomal instability pathway, which is better affected by chemotherapy [25]. That suggests that tumor pathogenesis and likely outcomes depend on the anatomical location. Therefore, more clinical trials are needed to confirm the underlying pathway.

Previous studies summarizing outcomes after right or left colectomy have shown mixed results. A study showed no significant differences in short- and long-term outcomes [26]. Comparable results, but only a higher readmission rate in the RCC group, similar to our trial, were noticed in the

**Table 3** Multivariable Cox regression analysis of overall and progression-free survival

Variable	Category	Overall survival		Progression-free survival	
		HR (95% CI)	P value	HR (95% CI)	P value
Tumor localization	RCC	1 (Reference)		1 (Reference)	
	LCC	0.801 (0.639–1.004)	0.054	0.890 (0.720–1.102)	.286
Age		1.037 (1.025–1.050)	0.001	1.025 (1.014–1.036)	0.001
Stage of disease	I	1 (Reference)		1 (Reference)	
	II	1.742 (1.051–2.888)	.031	1.923 (1.178–3.141)	0.009
	III	2.840 (1.743–4.627)	.000	3.380 (2.107–5.422)	0.001
	IV	12.702 (7.748–20.825)	.000	16.203 (10.004–26.243)	0.001
ASA score	ASA1-2	1 (Reference)		1 (Reference)	
	ASA3-4	1.499 (1.171–1.920)	0.001	1.485 (1.175–1.876)	0.001

HR hazards ratio, 95% CI 95%, ASA American Society of Anesthesiologists score

study of evaluation of laparoscopic surgery in hemicolectomies [27]. However, there are controversial data on postoperative complication rates in comparison to “traditional” resection for colon cancer, and complete mesocolic excision (CME) — that is similar to Japanese D3. The goal of this approach is to preserve the integrity of embryological planes and ensure a complete lymphadenectomy [28, 29]. To ensure proper staging of the disease, according to the Union for International Cancer Control (UICC) recommendations, a minimum of 12 lymph nodes should be removed and examined [30]. Typically, the right colon contains a significantly greater number of lymph nodes compared to the left [31]. Therefore, as fewer lymph nodes are normally in the left colon, it is commonly recommended to perform central vascular ligation (CVL) in left hemicolectomy to achieve CME and obtain the highest possible number of retrieved lymph nodes [29, 32]. Studies show that D3 right hemicolectomy also results in a larger harvested lymph node yield without increasing morbidity and even mortality [33, 34]. The need for CME in right colectomy surgery is therefore debated. Some authors claim that CME is linked to higher intraoperative organ injuries that lead to longer hospitalization and poorer short-term outcomes [35], but others report that there was no difference in overall complication rates with CME [36]. Nevertheless, recent studies and ongoing trial results have shown that extended lymphadenectomy has oncological benefits in colorectal cancer for better staging [35, 37]. Moreover, that results in decreased local recurrence rates and thus in lower overall mortality rates [29, 33].

Our study has some limitations. First, we excluded patients without primary anastomoses (for example patients with large left-sided tumors that may have had a Hartmann-type operation) as this could influence the results — taking into account the fact that most probably these patients may have been the most frail ones. Second, we did not evaluate the quality of surgery — although highly skilled colorectal surgeons with experience of at least 100 colectomies performed most of the surgeries and the complete mesocolic excision with high vascular ligation is the gold standard at both institutions. Moreover, we have not assessed the nutritional state of the patients and the molecular mutations of the cancer as well as the genetic and molecular and immunobiological factors. Additionally, we could not retract the data on adjuvant chemotherapy; this might have the effect on long-term survival. Finally, we did not have the data on the reasons for 90-day readmission.

## Conclusion

This study evaluated the short- and long-term outcomes for patients with right- and left-sided colon cancer. The results showed that people with right-sided cancer were

often older and had more comorbidities, although, both groups did not significantly vary in terms of postoperative morbidity, mortality, or short-term surgical outcomes. However, higher 5-year overall survival and disease-free survival were observed for the patients in the LCC group. Thus, age, comorbidities, and tumor stage are the main determinants of a patient’s prognosis after hemicolectomy. Further research is necessary to identify other possible factors affecting outcomes after right or left colectomy.

**Authors’ contribution** Conceptualization: Justas Kuliavas, Kęstutis Strupas, Audrius Dulskas, Tomas Poškus. Methodology: Justas Kuliavas, Audrius Dulskas, Marius Kryžauskas. Validation: Marius Kryžauskas, Justas Kuliavas; formal analysis, Justas Kuliavas, Kristina Marcinkevičiūtė, Augustinas Baušys, Klaudija Bičkaitė, Rimantas Baušys, Vilius Abeciūnas, Austėja Elžbieta Degutytė, Marius Kryžauskas, Eugenijus Stratilatovas, Audrius Dulskas, Tomas Poškus, Kęstutis Strupas. Investigation: Justas Kuliavas, Marius Kryžauskas, Audrius Dulskas, Tomas Poškus. Resources: Marius Kryžauskas, Tomas Poškus, Kęstutis Strupas, Justas Kuliavas, Audrius Dulskas, Augustinas Baušys, Eugenijus Stratilatovas. Data curation: Vilius Abeciūnas, Austėja Elžbieta Degutytė, Marius Kryžauskas, Justas Kuliavas, Augustinas Baušys. Writing—original draft preparation: Kristina Marcinkevičiūtė and Justas Kuliavas. Writing—review and editing: Kristina Marcinkevičiūtė, Justas Kuliavas, Audrius Dulskas, Augustinas Baušys, Marius Kryžauskas, Kęstutis Strupas, and Tomas Poškus. Visualization: Kristina Marcinkevičiūtė, Augustinas Baušys. Supervision: Tomas Poškus and Kęstutis Strupas.

**Data availability** Patients’ data is stored in the authors’ database. Data is not publicly available.

## Declarations

**Ethics approval** Vilnius Regional Ethics Committee approved the study (No. 2019/3-1116-608, 2019-03-20).

**Competing interests** The authors declare no competing interests.

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# Telementoring Experience for Complex Bariatric Operation—Laparoscopic Single-Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy (SADI-S)

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Received: 15 February 2024 / Revised: 21 March 2024 / Accepted: 21 March 2024  
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## Abstract

In a groundbreaking surgical collaboration, a team of surgeons in Lithuania successfully performed the first single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) operation under the remote telemonitoring guidance of a highly experienced surgeon from Spain.

The Lithuanian surgical team, comprising skilled bariatric surgeons, meticulously prepared for the SADI-S operation under the remote guidance of their Spanish proctor. Utilizing video conferencing and real-time communication, the mentor provided step-by-step instructions, shared insights, and addressed any concerns during the procedure. The mentor's extensive experience and guidance ensured a safe and successful surgical outcome.

This innovative approach not only demonstrates the potential of telemedicine in the field of complex bariatric surgeries but also highlights the power of international cooperation in advancing surgical techniques and patient care by using modern methods of telemedicine and proctorship.

**Keywords** SADI-S · Telemedicine · Proctorship · Telementoring · Bariatric surgery

## Introduction

The single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is a bariatric operation that was initially reported in 2007 [1]. SADI-S is a challenging bariatric procedure that requires special skills and is usually performed by skilled bariatric surgeons in specialized hospitals due to complicated hand-sewn anastomosis [2]. Typically, the learning time for SADI-S operation can vary depending on several factors, including the surgeon's experience,

the availability of mentorship, and the resources and support provided. However, the COVID-19 pandemic has posed additional obstacles to reduce the learning time of this operation. Therefore, new technologies and innovations were started to be used for distance learning [3]. This case report aims to demonstrate the feasibility of performing SADI-S operation through real-time telemonitoring by an experienced bariatric surgeon guiding colleague who has undergone the observation and assisting learning phases for this surgery.

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## Methods

The surgical procedure described in this study utilized a telemonitoring platform called “Vuzix” to facilitate remote guidance and mentorship. The operation took place in Vilnius, Lithuania, while the mentor Javier Osorio, an experienced surgeon, was located in Barcelona, Spain. The operating surgeon in Lithuania wore specialized smart glasses that allowed the mentor to view the surgical field on his computer screen. The telementoring platform was connected



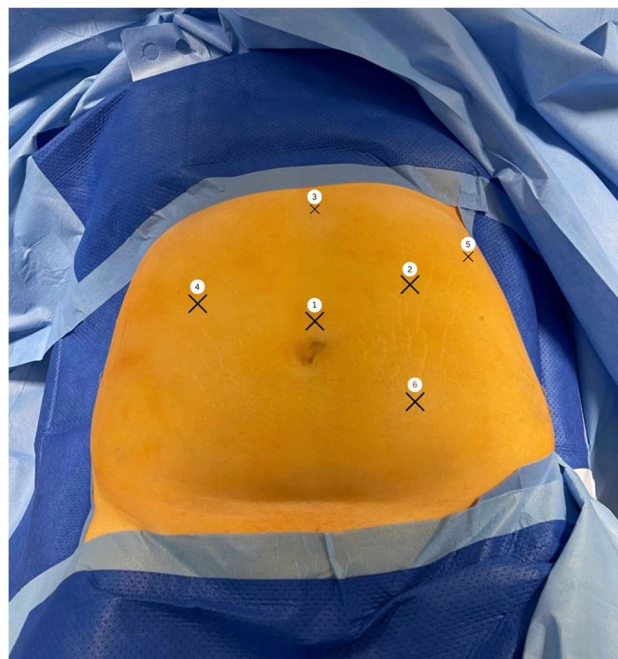
to a laparoscopic camera, providing a live stream of the surgical procedure to the mentor's screen. The mentor was able to guide the operating surgeon by marking dissection planes on the laparoscopic view, which were projected onto a small screen in the surgeon's glasses. Real-time communication between the surgeons was facilitated through an external microphone and speakers, enabling the mentor to provide verbal guidance, countertraction directions, and additional advice to the operating surgeon and his assistants (Fig. 1).

The mentor in this study (J.O.) was an experienced abdominal surgeon who has successfully performed more than 326 SADI-S operations and has been international bariatric mentor. The mentee, operating surgeon in this case, was also a qualified abdominal surgeon with significant experience in laparoscopic gastric operations, having performed approximately 400 gastric sleeve and gastric bypass procedures. Additionally, the mentee had attended a specific workshop on SADI-S and had the opportunity to observe four SADI-S operations, one of which he actively assisted in.

## Results

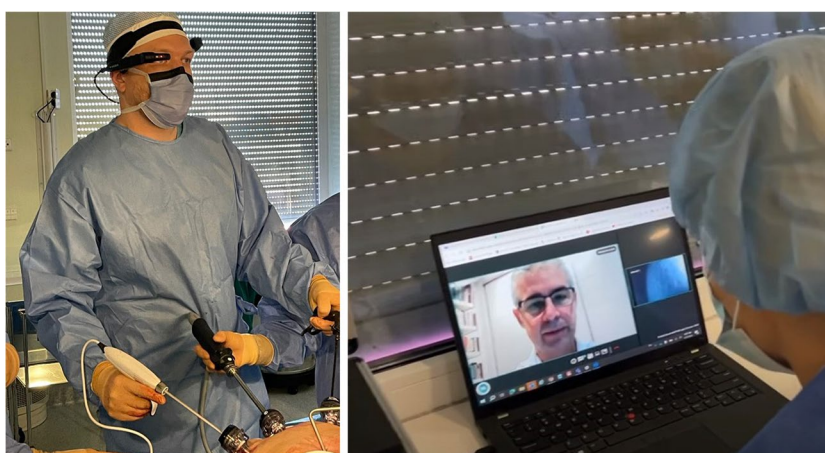
The patient was a 27-year-old female with a body mass index (BMI) of 42 (weight, 127 kg; height, 173 cm). She had a history of appendectomy and previous cesarean section (C-section). A standard SADI-S procedure was undertaken, which involved positioning the patient in a reverse Trendelenburg position at 30 degrees. The surgeon was positioned between the patient's legs, with the cameraman positioned on the left side and the first assistant on the right side. Five trocars were positioned during the procedure: a 12-mm trocar above the umbilicus for the 30-degree laparoscope, another 12-mm trocar on the left midclavicular line 5 cm below the costal margin, a 5-mm trocar below the xiphoid appendices for liver retraction, and a 5-mm trocar between the right anterior axillary and the right midclavicular line,

5 cm subcostally (Fig. 2). The surgical procedure began with the meticulous division of the omentum from the greater curvature in order to mobilize the pylorus and enhance access to the duodenum. Right gastric artery was identified and ligated. The duodenum was mobilized up to the right gastroepiploic artery which was also ligated. Following this, sleeve gastrectomy was performed with an approach from a lateral perspective. The greater curvature was divided from the omentum up to the left crus of the diaphragm. Additionally, the posterior wall of the stomach was carefully freed from any adhesions to the pancreas, ensuring a thorough and safe procedure. After completely mobilizing the fundus,



**Fig. 2** Trocars locations: 1 (camera); 2, 4, 6 size 12 mm; 3, 5 trocars—5 mm

**Fig. 1** Real-time communication between operating surgeon/mentee and experienced mentor via smart glasses, microphone, and speakers





a 36-Fr bougie was inserted through the mouth and guided to the duodenum under laparoscopic vision. Two 60-mm (green reload), linear surgical staplers were used to perform vertical resection. Subsequent firing was done using three 60-mm (blue reload), linear surgical staplers; after resection, we sutured the gastric sleeve using absorbable 2/0 barbed suture.

Following the previous steps, the duodenum was divided using an automatic linear stapler. Subsequently, a 12-mm trocar was inserted into the left lower quadrant for further access. A 12-mm port was chosen at number 6 in order to introduce a camera for better visualization if necessary. A precise measurement of 300 cm from the ileocecal junction was taken, and a meticulous two-layer ileo-duodenal anastomosis was performed. To ensure the integrity of the anastomosis, we conducted a thorough check for leaks using methylene blue, which yielded negative results, indicating a secure anastomosis. The resected portion of the stomach was then extracted through a 12-mm trocar site located on the left side. Lastly, no drains were left in the surgical site as part of the procedure.

In this study, a typical SADIS (single-anastomosis duodeno-ileal switch) procedure was performed following the technique suggested by Sánchez-Pernaute in 2007. However, there was a slight modification in the positioning of the limb, which was placed at a distance of 300 cm from the ileocecal valve. The anastomosis was meticulously created using a two-layer hand-sewn technique. The entire operation was completed within a duration of 180 min, with minimal blood loss. No drains were left in the surgical site. Importantly, there were no complications during the surgery, and there was no need to convert to open surgery.

Postoperatively, at the 3-month follow-up, the patient reported feeling well with no complaints or signs of any postoperative complications, loss of 19.5 kg (BMI index  $42 \geq 35$ ).

## Discussion

We showed that complex bariatric operation can be safely performed for the first time proctored remotely by an experienced surgeon using a telemonitoring system. The operation went well and there were no complications.

Telementoring in surgery has been present for almost 30 years, while early telementoring was challenging due to bandwidth limitations and the quality of video transmission or lack of necessary equipment, advancements in technology have progressively addressed these challenges [4]. Furthermore, the integration of artificial intelligence and augmented reality has the potential to further enhance the overall experience in surgical teleproctoring.

The COVID-19 pandemic underscored the significance of remote proctoring, enabling the continuation of the teaching and learning process in surgery during lockdown [5]. Therefore coaching due to telemonitoring system was found to be a more cost-effective and time-efficient alternative that minimizes travel for both surgeon and proctor compared to traditional in-person proctoring [6, 7]. This technology also permits instructors to devote more time to other tasks [8]. Moreover, using this approach would also result in considerable cost savings because telemedicine equipment is frequently reused for teleproctoring [9].

Telemonitoring by professional surgeons allows to spread identical quality of surgical treatment experience across different hospitals worldwide [10, 11]. Telementoring enables the experienced surgeon to advise the mentored surgeon in developing new or improving existing abilities [12, 13]. Furthermore, proctoring should enable for evaluation of the equipment, surgical team, and their ability to solve technical issues. Although some argue that more complex bariatric or revisional surgery should require the assistance of a trained colleague in the operating room [8, 14], we presented a case of a complex bariatric operation—SADI-S, for which prior short courses and long-distance remote guidance were sufficient. During the operation, proctor surgeons have discussed where it is the best to make an incision or other maneuver by plotting on a small monitor that is attached on the operating surgeon glasses. This makes the operation safe and ensures the quality of the operation [15]. Moreover, data in the literature show that teleproctoring results in a high level of surgeon satisfaction with no difference in complications rate [16]. That enhances surgeon confidence during surgery in the difficult situations [7]. Therefore, telementoring has the potential to guide and help to get surgical skills from far away maintaining good postoperative outcomes.

Telemonitoring system provides real-time verbal interaction that is particularly essential in the event of an unexpected intraoperative emergency, where the tutor can give the instructions for managing it [9, 17]. However, the proctor has no legal duty to act physically in the event of a potential difficulty in order to manage it. Thus, the medicolegal consequences of a proctor's active surgical participation are not well defined [18]. A meta-analysis concluded that, despite the possible disadvantages, telementoring learning in surgery may improve treatment outcomes, especially when on-site mentoring cannot be performed [19].

## Conclusions

This telemedicine experience demonstrates the feasibility and safety of conducting the SADI-S operation through real-time telemonitoring supervising by highly experienced mentor and performed by well trained surgeon. Also, our

innovative experience showcased the power technology in advancing of international surgical practices. The utilization of telemonitoring technologies and proctorship significantly reduced the learning period for SADI-S, overcoming the challenges posed by the COVID-19 pandemic.

## Declarations

**Ethics Approval** This article was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, which revised in 1983.

**Consent to Participate** The patient signed informed consent.

**Competing Interests** The authors declare no competing interests.

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## Article

# Self-Locking Polymeric Clips Are Safe for the Closure of Appendiceal Stump in Laparoscopic Appendectomy

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**Abstract:** *Background:* Closure of the appendix stump is critical to avoid serious postoperative complications. There are a number of options, but the best one has not been identified yet. The purpose of this study is to evaluate the outcomes of appendiceal stump closure using self-locking polymeric clips and endoloops. *Methods:* A retrospective analysis of the prospectively maintained database of patients with acute appendicitis was performed. Patient demographic details and surgical characteristics, including the duration of hospital stay, postoperative complications, and also the cost of the appendix stump closure, were recorded. Patients were divided into two groups according to the appendix stump closure method: the clips group if it was closed with self-locking polymeric clips and the loops group if Vicryl or PDS loops were used. Statistical analysis was performed using Pearson's chi-squared test, Wilcoxon rank sum (Mann–Whitney U) test, and Fisher's exact test in R statistical software package version 4.2.1. *Results:* 515 patients were included in the study from June 2016 to April 2021. There were no significant differences in terms of demographics ( $p$ -value in comparison of groups' sex  $> 0.99$ , age  $p$ -value 0.16), postoperative complications ( $p$ -value  $> 0.99$ ), histological findings ( $p$ -value 0.27), or length of hospital stays ( $p$ -value 0.18) between the two patient groups (clips group,  $N = 454$  and loops group,  $N = 61$ ). The price of operation while using different appendiceal stump closures is significantly different. In a laparoscopic appendectomy, one stump closure with self-locking clips costs 7.69 €, with Vicryl loops—91.35 €, with PDS loops—96.51 €, and with a stapler—514.50 €. *Conclusions:* Self-locking polymeric clips can be used for the safe and effective closure of an appendiceal stump. There were no significant differences in the postoperative time (30 days) or complication rates among patients in both (clips and loops) groups. Thus, this might be a technique to reduce expenses while maintaining good postoperative results after laparoscopic appendectomy.

**Keywords:** appendicitis; appendectomy; stump closure; polymeric clips; endoloops



**Citation:** Marcinkeviciute, K.; Luksaite-Lukste, R.; Jasiunas, E.; Poskus, T. Self-Locking Polymeric Clips Are Safe for the Closure of Appendiceal Stump in Laparoscopic Appendectomy. *Medicina* **2023**, *59*, 533. <https://doi.org/10.3390/medicina59030533>

Academic Editors: Žilvinas Dambrauskas and Claudio Gambardella

Received: 2 February 2023

Revised: 3 March 2023

Accepted: 7 March 2023

Published: 9 March 2023



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## 1. Introduction

Appendicitis is a common surgical cause of acute abdomen and affects approximately 7% of the population in their lifetime [1]. Laparoscopic appendectomy is a gold standard for acute appendicitis [2]. Laparoscopic appendectomy is superior to open appendectomy due to shorter hospitalization time, reduced postoperative analgesic requirement, early food tolerance, quicker return to work, and lower risk of wound infection [3,4]. Moreover, laparoscopy allows for greater visualization and identification of various abdominal disorders that might simulate acute appendicitis, especially if the vermiform appendix is found nonaltered [5–8]. Closing the appendiceal stump is a critical step in an appendectomy to avoid major complications, such as postoperative fistula, peritonitis, and sepsis [9]. Several closure techniques are reported in the literature, including using a stapler, endoloop, titanium clips, nonabsorbable polymer clips (hem-o-Lok clip), handcrafted loops,

transsection using Ligasure, bipolar cautery, or harmonic scalpel [10–12]. In recent years clipless/sutureless techniques using a harmonic scalpel for appendiceal stump closure gained popularity and were also proven to be safe and sufficient [12]. A recent systematic review concluded that in terms of the length of stay and postoperative complications, such as wound infection or postoperative ileus, a harmonic scalpel is similar. It has the only advantage of reducing the duration of the operation in comparison with conventional laparoscopic appendectomy techniques [13]. The main drawback of the harmonic scalpel is the price of disposable hand equipment [13]. However, there is no consensus on the technical method for closing the appendix stump. Moreover, the main disadvantage of laparoscopic appendectomy is the higher cost of the surgery due to the expensive equipment used compared to open surgery [14]. Despite great postoperative results, due to the high cost, there is no clinical evidence to justify the regular use of endoscopic staplers [15]. The routine practice of our department is to perform the closure of the appendiceal stump using polymeric self-locking clips. A polymeric clip is a V-shaped clip made of a nonabsorbable polymer that is available in a variety of sizes. It is utilized to seal off bleeding arteries or tissue structures. In laparoscopic surgeries, it may ligate tissue up to 10 mm using a 5 mm trocar or up to 16 mm through a 10 mm trocar [16]. We use three polymeric clips in laparoscopic appendectomy in our center: Two clips are placed on the base of the appendicitis while a third clip is above the appendicitis, and finally, we cut between the clips and remove the appendicitis. In cases when polymeric clips cannot be safely applied on the appendiceal stump (when the diameter of the vermiform appendix is too large for polymeric clips, or it is technically difficult to apply them), endoloops are used. Vicryl (polyglactin) or PDS (polydioxanone) can be used to make a loop ligature. When the loop is in place, the loop is tightened, thereby pinching and securing the knot [16]. We use three PDS loops as a standard or a mix of one PDS and two Vicryl loops due to it being more cost-effective. Since the use of polymeric clips is not a standard treatment method for all appendiceal stump closure in laparoscopic appendectomy [17], our study aimed to evaluate its effectiveness and safety for appendiceal stump closure.

## 2. Methods

### 2.1. Study Population

We performed a retrospective analysis of the prospectively maintained database. The study was approved by the Vilnius Regional Ethics Committee (2019/3-1107-610) in March 2019. All patients treated for acute appendicitis at a tertiary care hospital of Vilnius University Santara clinics (Lithuania) were entered into the prospectively maintained database [18]. Patients who underwent laparoscopic surgery for acute appendicitis from June 2016 to April 2021 and met the inclusion criteria (Table 1) were included in this study. The diagnosis of acute appendicitis was made according to the basis of clinical examination, the leukocytosis and high C-reactive protein in laboratory tests, transabdominal ultrasound, and computed tomography if the diagnosis was suspected clinically, but there were not enough signs to confirm or exclude the diagnosis of acute appendicitis. In this study, patients were not divided into groups according to the appendiceal stump closure technique before the operation. As it is a retrospective analysis of patients who were prospectively registered in the database, our study had no impact on the assignment of patients to one group or another. When laparoscopic appendectomies were introduced in Lithuania, polymeric clips were used to close the appendiceal stump, and they are still applied as a standard in our hospital today. Therefore, alternatives for polymeric clips (endoloops or stapler) for appendiceal stump closure are most commonly used when the surgeon decides at the time of surgery that the closure of the appendiceal stump is not possible with a polymeric clip. As a standard in our center, endoloops are used due to their lower price compared with staplers.

**Table 1.** Inclusion and exclusion criteria for a retrospective study.

Inclusion Criteria	Exclusion Criteria
Adults $\geq$ 18 years of age Patients with acute appendicitis diagnosis Patients underwent laparoscopic appendectomy	Patients treated conservatively Patients underwent open appendectomy Patients who needed a stapler application

## 2.2. Data Collection

Information obtained from the database included patient demographic characteristics, such as sex and age, with surgical characteristics, including closure method of the appendiceal stump (self-locking polymeric clips or endoloops), with outcomes, such as complications, histological findings, and length of stay, as well as financial outcomes of stump closure method. The patients were divided into two groups based on the performed stump closure technique: self-locking polymeric clips (clips group) and endoloops (loops group). A 30-day follow-up was completed for all patients.

## 2.3. Hypothesis and Outcomes Measures

We hypothesized that self-locking clips and endoloops are equally safe and effective for appendiceal stump closure. The primary outcome of this study was the rate of complications in the two groups: the clips group and the endoloops group. The secondary outcomes were sex, age, histological findings, hospitalization length, Clavien–Dindo grade, and the cost of operation.

## 2.4. Operative Technique

After the induction of general anesthesia, patients were placed supine position. A Veress needle was introduced below the umbilicus, and CO<sub>2</sub> was insufflated at a pressure of 10–12 mm Hg. In all cases, laparoscopic appendectomy was performed with 3 inserted trocars (5 mm, 10 mm, and 12 mm trocars). The appendicitis was identified, periappendiceal or pericecal adhesions were lysed, and the mesoappendix was dissected with the polymeric or titanium clip placed on the appendiceal artery. The base of the appendicitis was ligated with 3 XL polymeric clips or with 3 PDS (or in some cases, 3 Vicryl loops or 1 PDS and 2 Vicryl loops) according to the surgeon's choice. Then, appendicitis was divided with the scissors distal to the clips or loops and removed through a 12 mm port.

## 2.5. Statistical Analysis

Statistical analyses were performed using R statistical software package version 4.2.1 (23 June 2022 © The R Foundation for Statistical Computing), Rstudio 1 July 2022 Build 554 © 2009–2022 Rstudio, PBC. Interval and ratio variables were described by means and standard deviation (SD), by medians, first quartiles (Q1), and third quartiles (Q3). Nominal and ordinal variables were characterized by frequencies and percentages across the corresponding subset of the sample. Shapiro–Wilk and Kolmogorov–Smirnov (K–S) tests we used to check the data for normality.

To compare differences between two independent groups when the variables in these groups were either ordinal or continuous but not normally distributed, we used Pearson's chi-squared test; Wilcoxon rank sum (Mann–Whitney U) test; and Fisher's exact test.

To measure the effect size and direction between a dichotomous (binary) variable and a continuous variable, unsatisfying the condition for normal distribution, we used the rank biserial correlation (rrb). To measure the association of categorical variables, we used Cramér's V effect size. We will assume that when rrb (Cramér's V) = 0.01–<0.30, we have a small effect; when rrb (Cramér's V)  $\geq$  0.31–<0.60, we have a moderate effect; and when rrb (Cramér's V)  $\geq$  0.61–1.00, we have a large effect.

### 3. Results

Six hundred and fifty-four patients with acute appendicitis diagnosis were first identified. A total of 542 patients underwent an operation, while 112 were treated conservatively and were not included in this study. A total of 27 patients were excluded because they underwent open appendectomy due to conversion after the complicated laparoscopic operation, and 515 patients were finally included in the study (Figure 1).

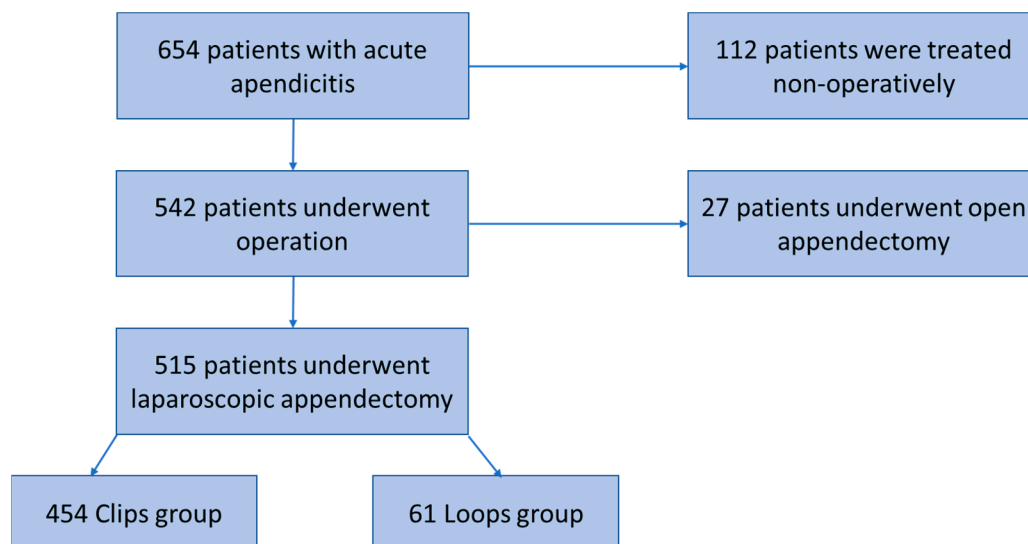


Figure 1. Flowchart of patients’ selection.

They were divided into two groups according to the choice of closure methods of the appendiceal stump in the performed laparoscopic appendectomy: self-locking polymeric clips (clips group) (454 patients) and endoloops (loops group) (61 patients).

The demographic and clinical characteristics of the groups are presented in Table 2. There were no statistically significant differences between the groups in sex, age, or histological findings.

Table 2. Clinical characteristics of two groups (clips group and loops group) of patients who underwent laparoscopic appendectomy.

Variable	N	Closure Method of the Appendix Stump			p-Value <sup>2</sup>
		Overall, N = 515 <sup>1</sup>	Clip, N = 454 <sup>1</sup>	Loop, N = 61 <sup>1</sup>	
Sex	515				>0.99
Female		245 (48%)	216 (48%)	29 (48%)	
Male		270 (52%)	238 (52%)	32 (52%)	
Age	515	37 (15)	36 (15)	40 (17)	0.16
Histological findings	515				0.27
Early changes		15 (2.9%)	14 (3.1%)	1 (1.6%)	
Secondary changes		6 (1.2%)	5 (1.1%)	1 (1.6%)	
Phlegmonous appendicitis		338 (66%)	304 (67%)	34 (56%)	
Gangrenous appendicitis		105 (20%)	89 (20%)	16 (26%)	
Perforated appendicitis		51 (9.9%)	42 (9.3%)	9 (15%)	

<sup>1</sup> Mean (SD) or Frequency (%). <sup>2</sup> Pearson’s chi-squared test; Wilcoxon rank sum test; and Fisher’s exact test.

A total of 515 patients underwent laparoscopic appendectomy and were followed 30 days after the operation. Table 3 presents the outcomes of the groups. There were no statistically significant differences in outcomes between the clips group and the loops group (p-value > 0.99). The 30-day complication rates were low at 1.8% and 1.6% in each group, respectively.



**Table 3.** Characteristics of patients’ groups and complications characteristics.

Variable	N	Closure Method of the Appendix Stump			p-Value <sup>2</sup>
		Overall, N = 515 <sup>1</sup>	Clip, N = 454 <sup>1</sup>	Loop, N = 61 <sup>1</sup>	
Complications	515				>0.99
Complications: No		506 (98%)	446 (98%)	60 (98%)	
Complications: Yes		9 (1.7%)	8 (1.8%)	1 (1.6%)	
Length of stay	515	3.15 (1.81)	3.09 (1.72)	3.61 (2.36)	0.18

<sup>1</sup> Mean (SD) or Frequency (%). <sup>2</sup> Pearson’s Chi-squared test; Wilcoxon rank sum test; Fisher’s exact test.

Table 4 presents the exact complications, Clavien–Dindo (C–D) grade, and histological diagnosis of each complication in both (clips and loops) groups. Hemoperitoneum was treated with a repeated operation. The blood was removed from the abdominal cavity; however, a clear source of bleeding was not identified. Abscesses were drained percutaneously. The abdominal wall ligature fistula was treated conservatively and healed. Wound infection, typhlitis, or postoperative fever was treated conservatively with a 10-day course of antibiotics (amoxicillin with clavulanic acid with metronidazole).

**Table 4.** Complications of the patients in the groups. C–D grade—complication grade according to Clavien–Dindo classification.

Clips Group, N = 454			Loops Group, N = 61		
Complication	C–D Grade	Histological Diagnosis	Complication	C–D Grade	Histological Diagnosis
Wound infection	1	Phlegmonous appendicitis	Postoperative fever	1	Perforated appendicitis
Hemoperitoneum, anemia	3b	Early changes			
Intra-abdominal abscess	2	Secondary changes			
Intra-abdominal abscess	2	Perforated appendicitis			
Abdominal wall ligature fistulae	1	Phlegmonous appendicitis			
Intra-abdominal abscess	2	Gangrenous appendicitis			
Typhlitis	2	Perforated appendicitis			
Postoperative fever	1	Perforated appendicitis			

The costs of the appendiceal stump closures are presented in Table 5. We calculated the hypothetical costs of the procedures. We use 3 polymeric clips in one laparoscopic appendectomy, while 5 clips in one unit cost 7.69 €, and we use 3 Vicryl or PDS loops, which are packaged one at a time, and one loop costs 30.45 € and 32.17 €, respectively. If all appendiceal stump closures were performed using clips, the cost of stump closure of one operation performed would be 7.69 €; if Vicryl loops were used, the cost would be 91.35 €; if PDS loops were used, the cost would be 96.51 €, as 3 loops are used; and if a stapler was used, the cost would be 514.50 €.

**Table 5.** Cost of different closure methods of appendix stump.

Closure Methods of the Appendix Stump	Cost (€)/Unit	Cost (€)/Surgery	Cost (€)/515 Patients
Self-locking polymeric clip	7.69	7.69	3960.35
Vicryl loop	30.45	91.35	47,045.25
PDS loop	32.17	96.51	49,702.65
Echelon stapler (FlexTM 45)	514.50	514.50	264,967.50

#### 4. Discussion

We found that the appendiceal stump can be safely closed using self-locking polymeric clips. The rate of postoperative complications in patients using clip closures and loop closures was low and neither clinically nor statistically significantly different (1.8 vs. 1.6%). Moreover, there are no statistically significant differences or any more significant effect

sizes between the two groups of different closure methods of the appendix stump and histological findings, patients' sex, patients' age, and the number of hospitalization days.

Acute appendicitis is still often misdiagnosed, and the negative appendectomy rate remains high [19]. In most studies, the negative appendectomy rate is less than 10% [20,21], but in some reported studies, it is higher—about 10–15% [9] and can exceed 20% [19]. A negative appendectomy rate is not reported in our study because in our database [18], only patients with a confirmed diagnosis of acute appendicitis who underwent laparoscopic appendectomy were included. Patients with a negative diagnosis of acute appendicitis were not included in the database; therefore, we could not count the rate of negative appendectomy. However, our hospital's prior experience revealed a 22.9% negative appendectomy rate when the diagnosis was based on laboratory tests and abdominal ultrasound [19]. The World Society of Emergency Surgery (WSES) recommends that an abdomen ultrasound should be used as the first-line radiological modality for suspected acute appendicitis [22]. However, in recent years, a decreasing trend of negative appendectomies has been observed due to using improved diagnostics tools, such as CT scans and Alvarado scoring, additionally as laboratory tests and abdomen ultrasounds [18,23–25]. Therefore, since January 2016, a CT scan was added to the diagnostic protocol in patients in whom diagnosis cannot be made using ultrasound. Since then, we reported a negative appendectomy rate of 4.2% [18]. If the correct diagnosis is made, unnecessary investigations and surgery are avoided. Thus, both additional hospital costs and potential complications during operation are avoided.

In the recent decade, nonoperative management of acute appendicitis is gaining more popularity due to reducing the possible number of complications after laparoscopic appendectomy and especially since some of them can be false positives and unnecessary [26]. Only those patients with a clinical diagnosis of localized appendicitis who do not have diffuse peritonitis or radiological signs of a large abscess, phlegmon, perforation, or tumor could be managed nonoperatively with an antibiotics course [27]. However, nonsurgical treatment of nonperforated appendicitis is not standardized and is used only in trials [28]. Moreover, nonoperative treatment was related to a higher rate of abscess, readmission, and total healthcare costs in comparison to surgical treatment and the cost of operation and possible complications [29]. Therefore, surgical treatment of acute appendicitis still remains the first-line choice for the management of acute appendicitis.

Appendiceal stump closure is a critical step in appendectomy operation, as inappropriate appendiceal stump closure might result in major postoperative complications. A variety of stump closure methods in laparoscopic appendectomy are used in clinical practice. The most popular are loops, stapling devices, clips, or electrothermal devices [30]. However, there is no agreement on the technical method that should be used when closing the stump. Based on a recommendation for the choice of appendix stump closure, only the stapler should be used if the appendix base is inflamed. If the entire appendix cannot be visualized, a clip or stapler should be chosen. In addition, only if the appendix is mobilized, a clip, loop, or stapler can be used depending on the base thickness [17]. A recently performed meta-analysis showed that endoloops and endostaplers are safe for appendix stump closure and have no difference in postoperative complication rate [31]. While self-locking polymeric clips (also known as Hem-o-Lok clips) are a less prevalent option in laparoscopic appendectomy for stump closure and are more used for the closure of bleeding vessels or tissue structures [16], they were also proven to have advantages: They are safe, cheap, and easy to use [32]. Although the clip in the literature is considered to be an unsafe choice for an inflamed appendix base [17], or there is a need for further high-quality studies before polymeric clips can be suggested as the gold standard for appendiceal stump closure [33], 131 (29.3%) patients in the clips group in our study were with gangrenous or perforated appendicitis where appendix base is usually inflamed, and only 4 of them had postoperative complications. According to clinical trial findings, all technical variants, endoloop, self-locking polymeric clips, and endostapler, are equivalent in terms of postoperative complications [34,35]. The presented deep surgical site complication rate was 1.7% of patients [34]. Our study presents comparable complication rates—1.8% for

self-locking polymeric clips and 1.6% for endoloops. Moreover, the shortest operative time and the lowest price of the operation were noted in the study [34] if self-locking polymeric clips were used. Comparable results report recent studies where polymeric clips are cheaper and less time-consuming alternatives to other commonly used techniques, such as endoloops [16,36–41]. In one study [37], a lower rate of intra-abdominal surgical abscesses was reported while using polymeric clips. Another advantage of polymeric clips is the ability to apply them, as most surgeons have several years of experience with laparoscopic cholecystectomies where these polymeric clips are used [35].

Patients undergoing laparoscopic appendectomy had many advantages of short operative time, the possibility to examine other abdominal organs, shorter hospitalization, and lower rates of postoperative complications compared to open appendectomy [42–45]. Recent studies show that the conversion rate from laparoscopic appendectomy to open appendectomy is 2–4% [46,47]. Conversion rates may vary between studies due to differences in the frequency of previous surgeries and adhesions, ages, and varying severity of appendicitis [46]. According to our study, the rate is 5% (27 patients) (Figure 1). These patients were not included in our study, as we were focused on two techniques' (polymeric clips and endoloops) comparison of safety in laparoscopic appendectomies.

However, the main drawback of laparoscopic appendectomy discussed in the literature is the high price of it due to expensive equipment [15]. We compared the prices in our hospital and found that self-locking polymeric clips are 11.9 times cheaper than Vicryl, 12.55 times more than PDS loops, and 66.9 times cheaper than Echelon staplers per one laparoscopic appendectomy operation. Moreover, from 61 cases where endoloops were used in our center, Vicryl loops were used 18 times (30%), and the mixed-loop technique (Vicryl and PDS loops) was chosen 8 times (13%) due to the lower price compared to only using the standard PDS loops. Therefore, polymeric clips are not only safe and effective for perforated and nonperforated appendicitis, but they are also cost-effective. Moreover, a recent study reports that polymeric clip choice as an alternative to endoloops or staplers does not prolong operation and hospitalization time [48]. It could be an option to reduce the price of laparoscopic appendectomy.

Surgery is one of the most energy-intensive activities, actively contributing to climate change [49]. Reprocessing and remanufacturing allow for the reuse of some of the medical devices. Self-locking polymeric clips are used, and the small package could be recycled. However, staplers are large polymeric/metal instruments, which in most instances, would end in landfills and would not be reused or recycled. The package of Vicryl or PDS loops are similar to clips in terms of recycling and much smaller than staplers [50,51].

### *Limitations*

This is a retrospective analysis of a prospectively maintained database, so all drawbacks of a retrospective study are applied here. We did not count operative time. As laparoscopic appendectomy is one of the first operations performed by residents, we feel that the different time is related more to surgical experience than to the technique of appendiceal stump closure. From our database, it is not possible to distinguish whether the surgery was performed completely by the resident or by the attending physician. Another limitation of this study is the heterogeneous patient groups. Our study had no effect on the assignment of patients to one of two groups. In our hospital, polymeric clips for appendiceal stump closure are standard practice, and loops were used only in cases where polymeric clips were judged to be difficult to apply. However, we believe that even having these limitations, it is still possible to safely recommend further use of polymeric clips for the closure of the appendiceal stump.

### **5. Conclusions**

Self-locking polymeric clips for appendiceal stump closure are as safe as endoloops. As there were no significant differences in the postoperative period and complication rates among these patients, this might be a way to reduce hospital costs while maintaining good

postoperative outcomes after laparoscopic appendectomy. Our retrospective analysis with a representative number of patients highlights the feasibility of polymeric clips for the closure of the appendicitis stump in laparoscopic appendectomy. Our study also highlights the huge cost difference, ranging from 11.9 to 66.9 times lower cost, when using polymer clips instead of their alternative—loops (PDS or Vicryl) or stapler.

**Author Contributions:** Conceptualization, T.P. and K.M.; methodology, R.L.-L.; software, E.J.; validation, T.P.; formal analysis, E.J.; investigation, K.M., R.L.-L. and T.P.; resources, R.L.-L. and T.P.; data curation, R.L.-L. and T.P.; writing—original draft preparation, K.M.; writing—review and editing, K.M. and T.P.; visualization, K.M.; supervision, T.P.; project administration, T.P.; funding acquisition, T.P. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Vilnius Regional Ethics Committee (2019/3-1107-610) in March 2019.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are openly available. <https://doi.org/10.3390/jcm10112456> (accessed on 8 December 2022), reference number in this article—[16].

**Conflicts of Interest:** The authors declare no conflict of interest.

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Case Report

# McKittrick–Wheelock Syndrome: A Case Report

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**Abstract:** An adenoma is the most typical large bowel tumor found in 30% of all screening colonoscopies. However, it is often asymptomatic but sometimes might lead to abdominal pain or bleeding of the rectum. Critical electrolyte disbalance and acute kidney injury caused by secretory diarrhea is an untypical clinical manifestation of adenoma. It has rarely been reported in the literature and is defined as McKittrick–Wheelock syndrome. A 61-year-old patient was hospitalized for heavy dyselectrolytemia, diarrhea, acute kidney injury, sepsis, and fever. After the renal function was corrected and electrolyte imbalance persisted, visual instrumental diagnostics tests revealed a large tumor in the sigmoid colon. Subsequently, the patient underwent surgical resection, which exhibited evidence of tubulovillous adenoma on pathology. The atypical signs of McKittrick–Wheelock syndrome and comorbidities can make the diagnostics challenging. When severe hyponatremia and hypokalemia are followed by persistent mucous diarrhea, the clinicians should suspect MWS as a possible reason for it.

**Keywords:** McKittrick–Wheelock syndrome; electrolyte imbalance; tubulovillous adenoma; villous adenoma



**Citation:** Marcinkevičiūtė, K.; Kryžauskas, M.; Poškus, T. McKittrick–Wheelock Syndrome: A Case Report. *Medicina* **2023**, *59*, 633. <https://doi.org/10.3390/medicina59030633>

Academic Editor: Henrik Falhammar

Received: 20 January 2023

Revised: 16 March 2023

Accepted: 20 March 2023

Published: 22 March 2023



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## 1. Introduction

An adenoma is an epithelial tumor with a glandular organization [1]. Adenomas are diagnosed in approximately one third of all performed screening colonoscopies [2]. Pathologic glandular architecture defines adenomas as tubular, villous, or tubulovillous [2]. Most villous adenomas are located in the sigmoid colon or rectum [3]. Less than 3% of all large villous adenomas tend to show hypersecretory function [4–6].

The extraordinary condition known as McKittrick–Wheelock syndrome (MWS) has been reported in the literature as electrolyte and fluid depletion related to secretory diarrhea which is caused by a large villous tumor in the colon or rectum [7]. The largest systematic study revealed a long duration of symptoms and severe electrolyte imbalances for patients with MWS [8]. However, the real prevalence of MWS in combination with colon adenoma is unknown [8,9].

In this paper, we report the case of a patient with large bowel adenoma which caused McKittrick–Wheelock syndrome.

## 2. Case Report

A 61-year-old female patient had a history of pulmonary tuberculosis in 2010. There were no signs of disease relapse, and the patient was considered recovered two years after the beginning of the treatment. The standard follow-up algorithm was used.

The patient complained of diarrhea, bloating, and general weakness in 2019. The symptoms lasted for at least one year. Slimy watery stools were up to 6–7 times a day. General routine tests were performed, and symptomatic treatment was prescribed. The general condition of the patient improved.

Later, the patient was treated due to acute kidney injury (AKI) and hypokalemia in 2020. A computed tomography (CT) scan was performed, which accidentally suspected a circularly thickened wall of the large bowel in the left lower quadrant. Therefore, a colonoscopy was performed. Atypical mucous membrane changes were identified, starting 20 cm from the anus, and continuing for about 30 cm long. Prominent, polypoid-shaped formations included large, confluent areas. A biopsy was taken. The lumen of the colon was slightly narrowed due to these formations and was full of continuous whitish mucus, but the endoscope could pass through it. The symptoms decreased after the conservative treatment. Unfortunately, the elective consultation with an abdominal surgeon did not take place due to the COVID-19 pandemic.

One year later, the patient was treated for urinary tract infection and hypokalemia. Additionally, the patient complained of a dry cough, general weakness, and a lack of appetite. The recurrence of pulmonary tuberculosis was not confirmed. The conservative treatment was successful.

Nevertheless, two weeks later, the patient was presented to our hospital's emergency department (ED) due to chest pain, shortness of breath, general weakness, nausea, diarrhea, and fever. Laboratory tests revealed high levels of urea, creatinine, deep hypokalemia, and elevated inflammatory markers, which all indicated AKI and sepsis. A chest computed tomography scan was performed due to the high level of D-dimers and acute respiratory system pathology was not identified. The patient was hospitalized in the internal medicine unit. Two hemodialyses were conducted, and kidney function was restored. Antibiotics were administered due to high inflammatory parameters. However, hypokalemia persisted despite performing hemodialysis and obtaining oral and intravenous potassium during the hospitalization period. Moreover, the patient still suffered from severe diarrhea.

Therefore, abdominal ultrasound was performed and showed intestinal changes with the thickened wall in the pelvis. An abdominal and pelvis computed tomography scan was performed to provide more detailed information. It revealed a possible tumor mass in the sigmoid colon (Figure 1). The patient underwent a colonoscopy, which revealed a large circular adenoma in the sigmoid colon of more than 20 cm long. A biopsy was taken at the time of the colonoscopy and the histological result was tubulovillous adenoma. Internal medicine doctors suspected MWS after all the examinations and surgical treatment was suggested for the patient.



**Figure 1.** An abdominal and pelvis computed tomography: tumor mass in the sigmoid colon.

The patient underwent a standard laparoscopic sigmoid resection with primary anastomosis. Postoperative total parenteral nutrition with bowel rest was admitted due to the

high risk of anastomotic leakage for the first 7 days [10]. Antibiotic therapy was continued after the operation due to the increased level of inflammatory markers. No surgical complications occurred for the patient. Diarrhea stopped for the patient and the electrolyte imbalance was solved. No further treatment was needed.

Macroscopically, the tumor was defined as a brownish, papillary, roughened tumor that had overgrown the mucosa (Figure 2). The final postoperative histological examination confirmed tubulovillous adenoma of the colon.



**Figure 2.** Macroscopic view of the tumor: brownish, papillary, roughened, and overgrows the mucosa.

### 3. Discussion

Several examples of massive villous adenoma with severe diarrhea leading to electrolyte abnormalities have been presented in the literature since it was initially reported by McKittrick and Wheelock in 1954 [7]. Orchard et al. summarized all reported cases and found out that MWS tends to affect older female patients slightly more often, as is the case with the patient in this presented case [8]. The syndrome is typically described as the triad of acute renal failure (ARF), electrolyte imbalance, and chronic diarrhea determined by a secretory colon neoplasm [11]. MWS is more likely to be present in large adenomas where they generate significant amounts of electrolyte-containing mucin. The pathophysiology could be explained by the fact that giant adenoma has a huge surface area, which secretes more fluid than the remaining normal rectal mucosa can reabsorb, and results in chronic watery diarrhea [12].

MWS often includes symptoms that result from an increased fluid secretion from a rectal villous adenoma. They might be different and non-specific, and that complicates early diagnostics. The main symptoms of MWS are dehydration, mucous diarrhea, and a large variety of symptoms determined by electrolyte imbalance [13]. Patients might present with hyponatremia that may manifest as lethargy, headache, weakness, nausea, muscle cramps, and seizures, or with hypokalemia that clinically occurs in fatigue, paresthesia, cramps, ileus, vomiting, hypotension, and cardiac arrhythmias [14,15]. Moreover, it is reported that a quarter of patients with MWS have electrocardiography changes [8]. The majority of patients initially arrive with diarrhea that is often watery or mucous. Moreover, patients have a long duration of symptoms and have a history of several previous hospitalizations [12]. Depending on the size and location of the adenoma, the fluid loss might reach 3 L per day. Bicarbonate loss from the stool, typical in secretory diarrhea cases, causes metabolic acidosis [16]. In our reported case, the patient was also admitted to the hospital due to electrolyte imbalance. However, there are referred cases in the literature

with an atypical presentation of MWS at the emergency department with rectal prolapse, dermatomyositis, or with encephalopathy due to severe hyponatremia [17,18].

The diagnostics might start with abdominal ultrasound followed by an abdomen and pelvis CT or magnetic resonance imaging (MRI). Later, a colonoscopy with biopsy for histological identification of the tumor should be performed. Because of the persistence of the symptoms and the first presumptions of other conditions, the diagnosis of MWS is frequently delayed, resulting in a severe state of volume depletion [8]. In the majority of reported cases, MWS was noticed due to electrolyte imbalance and AKI with abnormally high renal function parameters and only then was specified using visual diagnostics tests [8,19,20]. This diagnostic process was also observed in our case. The suspicion was first due to high levels of urea, creatinine, and severe hypokalemia; then, intestinal changes were noticed in abdominal ultrasound. The sigmoid colon location and the size of 20 cm of adenoma were confirmed with abdomen and pelvis CT. Consequently, tubulovillous adenoma was verified by biopsies during the colonoscopy.

Tumor removal is the cornerstone of MWS treatment. Once renal function and electrolyte imbalance are corrected, the excision of the tumor, whether with surgery or endoscopy, should be performed [5]. Recently published studies have shown an increase in the usage of minimally invasive procedures such as transanal endoscopic microsurgery, transanal minimally invasive surgery, endoscopic mucosal resection, and endoscopic submucosal dissection [21,22]. However, some authors noticed that the risk of recurrence is greater after minimally invasive operations [4,9,18]. Endoscopic techniques may be technically challenging due to the large size of the tumor in MWS patients [18]. In our case, laparoscopic-assisted surgery was chosen. The prognosis after the removal of the tumor is excellent [23].

#### 4. Conclusions

McKittrick–Wheelock syndrome is a rare and possibly fatal disorder. It usually presents with diarrhea, acute kidney injury, and metabolic abnormalities. Surgical treatment should be the first choice for patients with MWS.

**Author Contributions:** Conceptualization, K.M. and M.K.; investigation, M.K. and T.P.; writing—original draft preparation, K.M. and M.K.; writing—review and editing, K.M., M.K. and T.P.; visualization, K.M., M.K. and T.P.; supervision, M.K. and T.P.; project administration, T.P.; funding acquisition M.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approval from the Institutional Review Board was granted.

**Informed Consent Statement:** Patient consent was obtained.

**Data Availability Statement:** Data is contained within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

#### Abbreviations

MWS	McKittrick–Wheelock syndrome
ED	Emergency department
CT	Computed tomography
ARF	Acute renal failure
MRI	Magnetic resonance imaging

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Case Report

# Vermiform Appendix within Post-Laparoscopic Incisional Hernia: A Unique Case Report and Literature Review

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**Abstract:** *Background:* Appendicitis within incisional hernia is an extraordinarily rare postoperative complication with an incidence range from 0.08 to 1%. From the 14 cases that we found in the English literature, only three present appendixes vermiform in incisional hernia followed by laparoscopic surgery. Only two cases are treated minimally invasively by the laparoscopic approach. *Case presentation:* We introduce a 65-year-old man who had a laparoscopic sigmoid colon resection and had a lump found at the 12 mm trocar site in the right iliac area in the late postoperative phase. There were no complaints from the patient. A vermiform appendix was unexpectedly discovered in the sac of that incisional hernia during control CT scans performed by chemotherapists. Laparoscopic hernia repair without appendectomy was performed. Postoperative outcomes were excellent. *Conclusions:* Because of low incidence and a lack of distinctive clinical presentation of appendicitis within incisional hernia, there is a risk of delayed perioperative diagnosis and treatment. A CT scan might play an important role in verifying the diagnosis early. For better postoperative outcomes, if possible, laparoscopic surgery should be chosen.

**Keywords:** vermiform appendix; incisional hernia; port-site incisional hernia; laparoscopic hernia repair



**Citation:** Marcinkeviciute, K.; Makunaite, G.; Danys, D.; Strupas, K. Vermiform Appendix within Post-Laparoscopic Incisional Hernia: A Unique Case Report and Literature Review. *Medicina* **2023**, *59*, 538. <https://doi.org/10.3390/medicina59030538>

Academic Editor:  
Claudio Gambardella

Received: 3 February 2023  
Revised: 23 February 2023  
Accepted: 7 March 2023  
Published: 10 March 2023



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## 1. Introduction

An incisional hernia is the most frequent surgical complication, with an estimated frequency of 35% [1]. However, the incidence of an inflamed appendix within a hernial sac is very low and ranges from 0.08 to 1% [2]. From these, appendicitis within an inguinal or inguinoscrotal hernia is the most prevalent [3]. Only very few papers have been published reporting appendicitis within incisional hernias. We counted only 14 such cases worldwide in the literature (Table 1) and only 3 of them were in incisions of previous laparoscopic operations [4–6]. In fact, in all of these three mentioned cases, the vermiform appendix was inflamed and none of them followed the laparoscopic approach of hernioplasty [6]. According to this statistic, we present an extraordinary case of a non-inflamed appendix within an incisional hernia after laparoscopic sigmoid colon resection, which was repaired in a minimally invasive way.



**Table 1.** Previous cases of appendix within the incisional hernia.

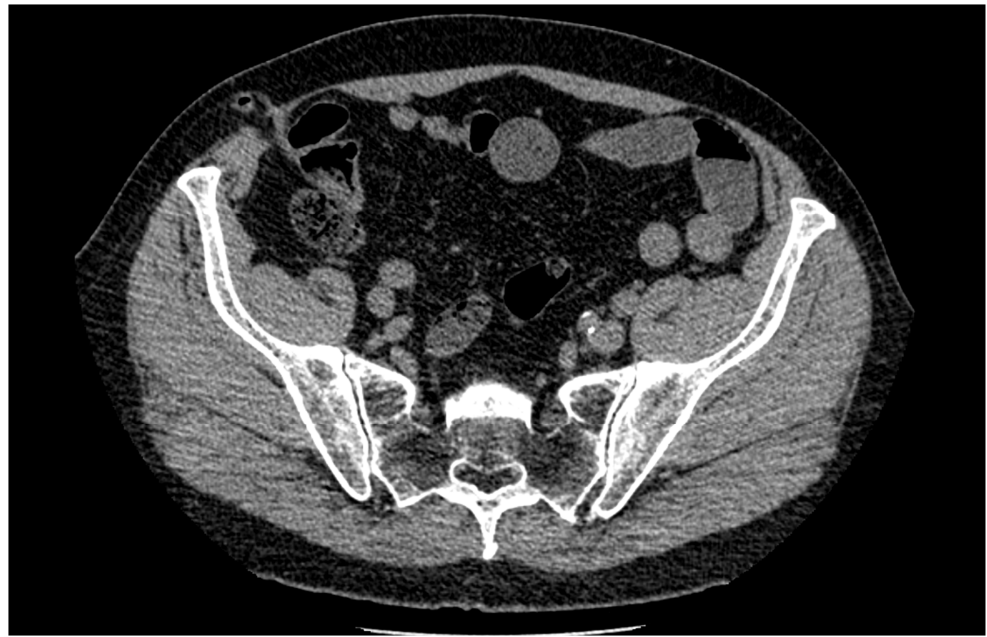
No	Authors	Previous Operation	Location of the Hernia	Type of Performed Operation	Normal or Altered Appendix
1	Erol T. et al. [7]	NA	NA	NA	Inflamed
2	Paudyal N. et al. [8]	Laparotomy with right-sided salpingectomy	Pfannenstiel incision	Open surgery	Inflamed
3	Lakhani DA. et al. [9]	Left total nephrectomy and renal transplantation	Right lower quadrant incisional hernia	Open surgery	Perforated
4	Molina G. et al. [10]	Open cholecystectomy	Kocher incision	Open surgery	Inflamed
5	Lam A. et al. [4]	Laparoscopic sterilization	Umbilical laparoscopic port site incision	Open surgery	Inflamed
6	Kler A. et al. [11]	Open total hysterectomy	Pfannenstiel incision	Open surgery	Normal
7	West C. et al. [12]	Open abdominal aortic aneurysm repair	Laparotomy incision	Open surgery	NA
8	Sugrue C. et al. [5]	Open cholecystectomy	Upper midline incisional hernia	Open surgery	Inflamed
9	Sugrue C. et al. [5]	Diagnostic laparoscopy and lavage	Five mm port site in the right iliac fossa	Open surgery	Inflamed
10	Galiñanes EL. et al. [13]	Total abdominal hysterectomy with right-sided oophorectomy	Pfannenstiel incision	Laparoscopic surgery	Inflamed
11	Dittmar Y. et al. [14]	Kidney transplantation	Right lower quadrant incisional hernia	Laparoscopic surgery	Inflamed
12	Singal R. et al. [15]	Open surgery of subsequent bone grafting from the right iliac crest	Previous operation incision	Open surgery	Inflamed
13	Menenakos Ch. et al. [6]	Laparoscopic low anterior rectal resection	Twelve mm trocar site incision in the right iliac fossa	Open surgery	Inflamed
14	McKay DW. et al. [16]	Open cholecystectomy	Kocher incision	Open surgery	Normal

NA—not available.

## 2. Case Report

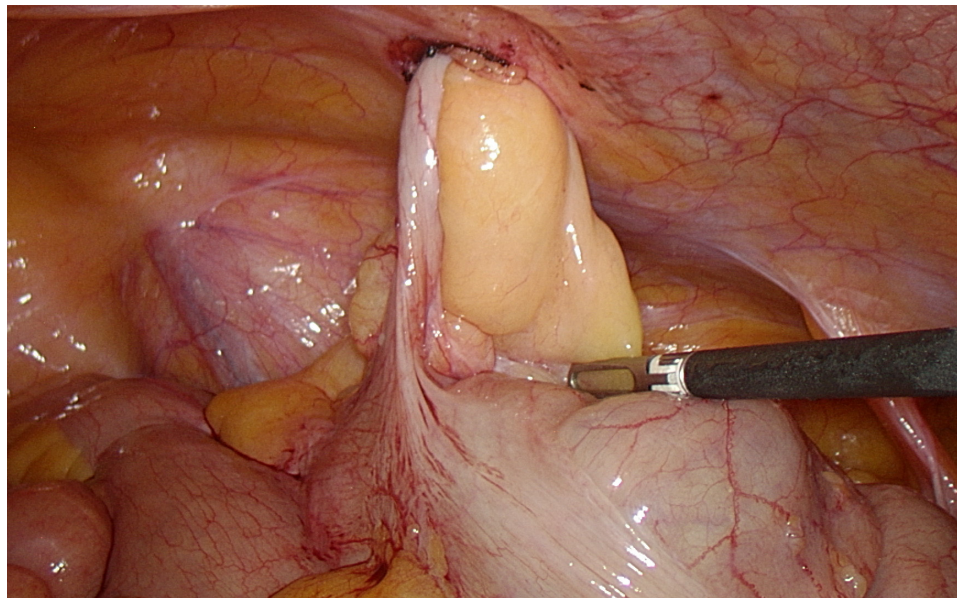
The patient gave their consent for this piece of research. Approval from the Institutional Review Board was granted.

We report a 65-year-old male patient with an appendix in an unusual post-laparoscopic hernia in the 12 mm trocar site in the right iliac fossa. He had only surgical history of laparoscopic sigmoid colon resection for sigmoid colon carcinoma (pT1N0M0) 3 years prior. In the early postoperative course, it went without complications. After that, the patient continued to be treated and monitored by chemotherapists. In the late postoperative period, a lump was detected at the 12 mm trocar site in the right iliac region of a previous surgery site that was observed as an incisional hernia. However, the patient had no complaints. During control CT scans by chemotherapists, a vermiform appendix was accidentally observed in the sac of that incisional hernia (Figure 1). Laboratory tests were normal, and the patient still had no other symptoms, except the lump. There were no signs of inflammation—clinically or radiologically; it was decided to perform a planned operation by the laparoscopic approach. Three trocars were placed in the abdominal cavity.



**Figure 1.** A vermiform appendix in the sac of the incisional hernia on a computed tomography scan.

Despite the absence of symptoms, it was decided to operate due to the contents in the hernia sac. During the operation, it was observed that the size of the hernial defect was 12 mm. The vermiform appendix and the mesentery had entered the incision of the trocar in the right iliac region (Figure 2). They were easily returned to the abdominal cavity; the adhesion fixing the appendix was cut and the aponeurosis here was sutured using a Berci needle with two stitches of Prolene. There were no indications for appendectomy and it was not performed. A hernia mesh was not used due to the small size of the defect, as well as due to the absence of risk factors such as obesity or heavy physical work. After this operation, the patient's condition was excellent, he had no complaints, and inflammatory indicators were within normal limits, so the next day he was discharged from the hospital. Early cosmetic results were also excellent (Figure 3). After a 5-week follow-up, the patient had no complaints and there were no signs of early relapse.



**Figure 2.** Vermiform appendix together with the mesentery within the previous trocar incision in the right iliac region.



**Figure 3.** Early cosmetic results after the operation.

### 3. Discussion

The incidence of port site hernia following laparoscopic surgery ranges from 0.38% to 5.4%, with a total incidence of 1.7% [17]. The bigger risk for hernia development is 10 mm and larger in diameter trocar incisions [18]. Although the location of the appendix in the abdominal cavity can be quite variable, its detection in a hernial sac is extremely rare [7]. In our case, the hernia with the appendix appeared at the location of a 12 mm trocar, which we routinely use for laparoscopic sigmoid colon resections. There is one more similar case in the literature, where in the same location incision, a hernia with an appendix inside of it formed after low rectum resection [6]. In another case report, a hernia with appendicitis in the hernia sac developed at the site of an umbilical 10 mm incision [4]. Even though the probability of postoperative incisional hernia formation at a site where an incision of less than 10 mm was made is extremely low, there is one case described in the literature where this phenomenon was observed at the site of a 5 mm trocar incision [5].

Appendicitis typically begins with widespread or periumbilical abdominal discomfort that radiates to the right lower quadrant and is usually followed by anorexia, nausea, vomiting, and fever [19]. Abdominal ultrasound evaluation due to its excellent specificity and sensitivity for diagnosing acute appendicitis is now generally accepted as a standard [14]. In situations with incisional hernia appendicitis, the classic appearance of appendicitis may be missing [11]. That leads to a worse prognosis of this situation because the diagnosis of appendicitis may be delayed and it might progress to a gangrenous form and even perforate, causing a life-threatening condition [8]. In these complicated cases, when appendicitis is located in the sac of the hernia, the diagnosis is usually verified by CT by suspecting other pathologies because of the unusual clinical presentation of appendicitis [10]. The clinical presentation of the reported examples in the literature is similar to that of an incarcerated hernia [11]. After a complicated hernia is identified, it is not standard procedure to submit the patient to a CT scan. However, our case shows that while the appendix is not inflamed, the symptoms might not appear and it can only be detected accidentally.

The preferred treatments for appendicitis within incisional hernia are appendectomy and hernia repair utilizing laparoscopic or open techniques [10]. The treatment of a non-inflamed appendix in the hernia sac is still controversial [9]. Most studies suggest surgical treatment tactics even though there are not enough clinical or radiological signs of acute appendicitis, while some others prefer avoiding operations due to possible complications if there is no data for inflammation of the appendix [11,13,16]. Since such cases are very few, there is a limitation of proof of the superiority of either choice. We did not perform an appendectomy because of the absence of signs of acute appendicitis: the laboratory tests and radiologic views seemed normal and when examined during laparoscopy, they did not appear altered. It was decided to avoid the possible complications after appendectomy—an intra-abdominal abscess, bleeding from the caecum, or appendix burst during the operation [20,21]. Moreover, the appendix has been established as an important component not only for the passage and elimination of waste matter in the lower digestive tract but also as part of the organism of stimulating immunity due to B- and T-lymphocyte-mediated response [22]. After performing any intervention in the abdominal cavity, where the anatomy is damaged, including appendectomy, adhesions form as a result [23]. Therefore, any other intervention would be more complicated due to adhesions.

During the same operation, not only appendix removal should be considered but also hernioplasty to fix the hernia. For the repair of a hernia defect, it is generally recommended to use a hernia mesh to restore the integrity of the abdominal wall through open or laparoscopic surgery. Over the years, the discussion in the literature about which method is superior is still continuing. In recent years, there has been an increase in the advantages of laparoscopic surgery in the postoperative period after hernia surgery [24]. In our case, surgery was not technically difficult to perform when the appendix was not inflamed and there were no indications to remove it. We chose laparoscopic surgery for hernia repair with all the advantages of minimally invasive treatment, less pain, shorter hospitalization time, faster healing, and better cosmetic outcomes. There are some surgical choices for abdominal wall defect closure: an intraperitoneal onlay mesh (IPOM), IPOM-plus (when the fascia defect is sutured before the mesh insertion), transabdominal preperitoneal (TAPP) repair, or intracorporeal suturing of the defect [25–27]. There is no ideal method; therefore, the knowledge of a wide range of surgical choices applied by surgeons of various skill levels is the ideal solution. The size of the hernia defect mainly determines the surgeon's choice. The laparoscopic approach for incisional hernias bigger than 15 cm is challenging, with a significant complication rate as a result for these patients' open hernia repair techniques (the onlay, sublay (retromuscular), or inlay methods) are recommended [28,29]. For smaller defects' repair, laparoscopic techniques could be considered. We did not use the mesh for hernia repair because of a small defect (only 12 mm) for which two stitches of Prolene were enough for its closure. Furthermore, when the hernia gap is smaller than 2 cm, the study [27] showed that hernia defect suturing without using a mesh is safe and the recurrence is low (4.1%). However, if in our case the defect size were bigger, the mentioned alternatives should have been considered.

To prevent incisional hernias, trocar sites with fascial defects of 10 mm or more, including the peritoneum, should be closed [30]. Opinions differ in the literature on whether a 5 mm trocar site defect should be closed [30,31]. Some studies report that in cases of paramedian locations and blunt-type trocars (conical, pyramidal, radially dilating, and non-bladed) usage, fascial closure is not crucial not only for 5 mm but also for 10 mm and 12 mm incisions [31]. However, most of the studies do not provide recommendations for 5 mm trocar site defect fascial closure [31]. Blunt-type trocars used for 5 mm trocar sites split the muscles instead of cutting them and in this way reduce the area of the facial defect [32,33]. The defect of 5 mm trocar insertion should be closed only if the defect might be extended due to manipulation in the abdomen [31].

#### 4. Conclusions

Appendicitis in an incisional hernia is an extremely rare occurrence. Because of the low frequency and unique clinical presentation, the risk of possible consequences owing



to delayed perioperative diagnosis and treatment is significant. All clinicians should evaluate it to avoid the consequences of delayed surgical treatment. CT scans might aid in early diagnosis. In addition, minimally invasive surgery should be considered. To avoid appendix vermiform or other structures within the incisional hernia after laparoscopic surgery, 10 mm and bigger abdominal defects should be closed.

**Author Contributions:** Conceptualization, K.M., G.M. and D.D.; investigation, G.M. and D.D.; writing—original draft preparation, K.M. and G.M.; writing—review and editing, K.M., G.M., D.D. and K.S.; visualization, K.M., G.M. and D.D.; supervision, D.D. and K.S.; project administration, K.S.; funding acquisition, K.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approval from the Institutional Review Board was granted.

**Informed Consent Statement:** Patient consent was obtained.

**Data Availability Statement:** Data is contained within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

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## Case Report

# Giant intrapulmonary solitary fibrous tumor with signs of malignancy

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## Abstract

Solitary fibrous tumor (SFT) is an extremely rare mesenchymal neoplasm usually detected in the pleura, which generally follows a benign course. The localization inside lung parenchyma has more rarely been reported. We present a case of a 51-year-old male with a dry cough, dyspnea, chest pain, and increased perspiration. Radiological images revealed a giant circumscribed mass on the right side of the chest. A transbronchial cryobiopsy of the lung was performed and revealed an SFT. The right upper lobectomy through lateral thoracotomy was performed. The pathological examination confirmed an SFT with a central zone of necrosis that is a sign of malignancy. At a 2-year follow-up, the patient is free of symptoms and with no evidence of recurrence. Although the intrapulmonary localization of an SFT is a rare entity, we should be aware of it as a potential malignant pulmonary neoplasm.

**Keywords:** solitary fibrous tumor; intrapulmonary tumor; lobectomy; lung cancer

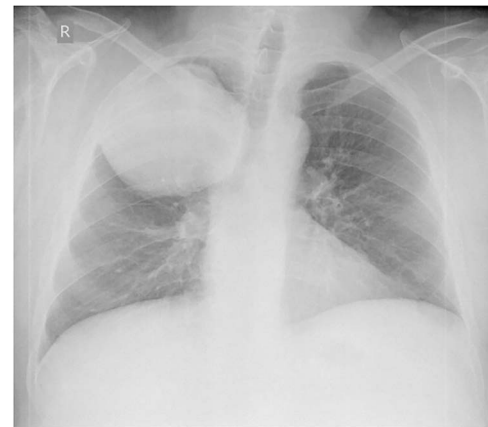
## Introduction

A solitary fibrous tumor (SFT) is an exceedingly rare neoplasm that is generally discovered in the pleura and is classified as a benign mass; however, sometimes it can progress into malignant [1]. The management of the tumor is surgical resection [2, 3]. There are only a few cases of intrapulmonary SFT presented in the literature. No reliable large-sample studies can identify the appropriate diagnostic, therapeutic, and follow-up steps for this tumor. We aimed to present a case of a giant SFT located inside the lung tissue and to report our experience in diagnostics and management.

## Case report

A 51-year-old man was admitted to the hospital because of a dry troublesome cough, pain on the right side of the chest, and increased perspiration. Symptoms lasted for 2 weeks. There had been no previous reports of fever, hemoptysis, chest discomfort, or specific sweats. He had a history of smoking (15 pack-years) and had no data of asbestos exposure.

Laboratory tests revealed leukocytosis  $-10.46$  ( $*10^9/l$ ) with 69.2% of neutrophils, but C-reactive protein was normal (1.37 mg/l). Chest X-ray showed a giant, homogeneous, clearly circumscribed opacity in the upper lobe of the right lung (Fig. 1).



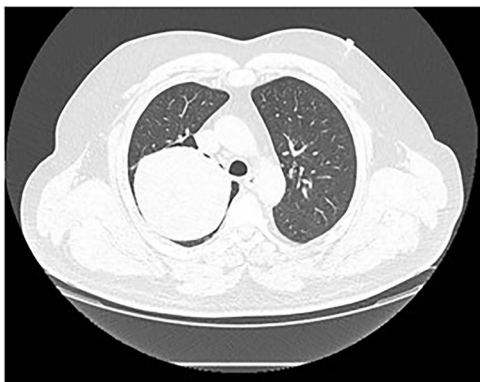
**Figure 1.** Anteroposterior chest X-ray. Giant, homogeneous, clearly circumscribed opacity in the upper part of the right chest.

Chest computed tomography (CT) revealed a well-defined solid nodule (Fig. 2). Bronchoscopy and transbronchial biopsy were performed. On pathology, no specific findings were found. The bronchoscopy was repeated, and a transbronchial cryobiopsy was performed. On pathology, an abundantly vascularized SFT was verified.

**Received:** December 16, 2023. **Accepted:** December 27, 2023

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**Figure 2.** Chest CT scan. A well-defined solid nodule of 10 cm in diameter in the right upper lobe.



**Figure 3.** The intrapulmonary tumor.

It was decided to perform pulmonary resection. A right upper lobectomy through lateral thoracotomy was performed, and the giant tumor (size  $10 \times 7 \times 9.5$  cm) inside of it was removed (Fig. 3). Macroscopically, the tumor appeared whitish with foci of fibrosis and a necrotic area ( $4.3 \times 2.5$  cm) in the center of it. The tumor consists of spindle cells arranged in irregular fibers in a fibrous stroma with thin-walled blood vessels. Focal areas of hypercellularity and necrosis (about 15%) were visible. Mitoses locally were up to 4/10 high-power field. Tumor cells were positive for STAT6 (+++) 100%, CD34 (+/+++)<sup>60%</sup>, and Ki67(++/+++)<sup>7%</sup> (Fig. 4). The final pathological diagnosis was SFT of the lung with malignancy evidence because of central necrosis, however, without increased focal mitotic activity.

The postoperative period was uneventful. On the 10th postoperative day the patient was discharged.

The follow-up was considered at 1, 6, 12, and 24 months after the discharge. At follow-up, the patient was doing well and was free of symptoms. There was no evidence of recurrence on the chest CT scan.

## Discussion

We have reported a rare case of a giant SFT with signs of malignancy in a nontypical place.

SFTs are composed of spindle-shaped cells and were originally considered neoplasia of the mesothelium because of their

propensity to arise from the pleura and mediastinum. In the original description by Klemperer and Coleman in 1931 it was called a “localized mesothelioma” [4]. Since its classic description, SFTs have been described in multiple extraserosal tissues including the lung, liver, thyroid, paranasal sinuses, and orbit, making it less likely to be derived from mesothelium, and more likely to be from a fibroblastic differentiated cell type in the submesothelial mesenchyme [5].

The majority of SFTs are benign; however, patients with malignant SFT present with larger tumors (bigger than 10 cm) and tend to be symptomatic [3, 6]. In the presented case, the symptomatic patient, and the big tumor size (10 cm) suggested a possible malignancy.

SFTs are characterized by haphazardly arranged fibroblast-like cells, indistinct nucleoli, prominent vasculature with perivascular fibrosis, and variable stromal collagen. Microscopically SFT shows a “patternless pattern” with abundant collagen in between cells of the tumor [7].

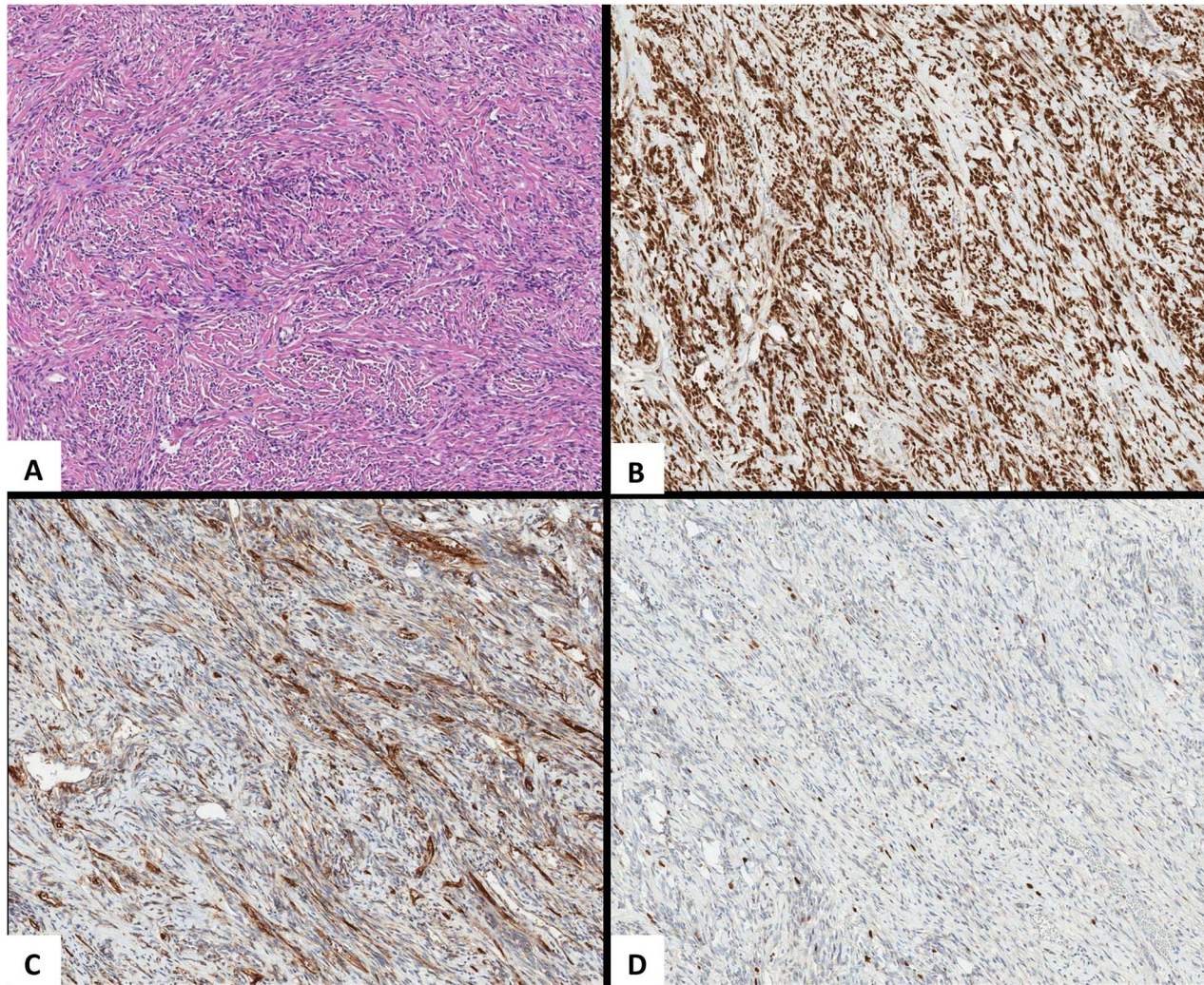
Although there are no definite criteria for malignancy, the 2013 World Health Organization classification recognizes that hypercellularity, moderate cellular atypia, >4 mitoses per 10 high-power fields, necrosis, nuclear pleomorphism, high MIB-1 staining, and infiltrative margins are histopathologic markers of malignancy and a more aggressive type of SFT [8]. SFTs have a particular pattern of immunohistochemical staining in addition to their normal light microscopic appearance [8]. Tumor cells are positive for vimentin, CD34, CD99, and Bcl2, but SFT is negative for cytokeratin, desmin, alpha-smooth muscle actin, or S100 protein cytokeratin, which are expressed in mesotheliomas. These markers help to differentiate those tumors from others [9, 10]. STAT6 is also a very sensitive and specific immunohistochemical marker for SFT [11]. The expression of Ki67 is strongly associated with malignant tumor cell proliferation and growth [12]. In the reported case, the tumor was positive for STAT6 (+++) 100%, CD34 (+/+++)<sup>60%</sup>, and Ki67(++/+++)<sup>7%</sup>. Since Ki67 was not expressed, the tumor tended to look benign; however, the clear positive expression of STAT6 and CD34 supported SFT diagnosis.

Surgical management is the gold standard of treatment for intrapulmonary SFTs [2, 3]. The technique of the surgery mainly depends on the size of the tumor. Certain publications propose thoracoscopic surgery for tumors <5 cm in size, whereas bigger tumors can be removed through a thoracotomy [13]. In the presented case, the tumor was big, so an open lobectomy was carried out.

The prognosis of SFTs depends on pathologic findings. The important prognostic factor associated with overall survival is a free resection margin [2]. In general, the 10-year overall survival rate is up to 94% [14]. Multicenter analysis revealed a significant correlation between metastasis and a larger than 10 cm tumor size with pathological signs of malignancy [15]. In the reported case, central zone of necrosis indicates tumor malignancy and could be related to a higher risk of recurrence. However, during the 2-year follow-up, there was no evidence of recurrence.

We presented an extremely rare case of intrapulmonary SFT with some signs of malignancy. Although SFTs usually have quite a favorable prognosis, some of them might progress locally or metastasize. A careful longer follow-up is required, especially for patients with positive resection margins, larger tumors, and presented malignancy signs.





**Figure 4.** Pathological images. (A) HEX10. An SFT is composed of spindle-shaped cells with indistinct cell borders arranged haphazardly or in short, ill-defined fascicles. (B) STAT6x10. Highly sensitive (98%–100%) and specific (100%) nuclear marker for SFT at all anatomical locations, regardless of tumor morphology. (C) CD34x10. An SFT with limited membranous CD34 expression. (D) Ki-67x10. An SFT, Ki-67 (nuclear marker of cell proliferation) expression.

### Conflict of interest statement

None declared.

### Funding

None declared.

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# Pancreatic Mucinous Cystic Neoplasm with Associated Invasive Carcinoma: A Case Report and Literature Review

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**Abstract.** *Background.* Pancreatic mucinous cystic neoplasm (PMCN) with associated invasive carcinoma is a rare entity. According to the World Health Organisation (WHO) 2010, PMCN with associated invasive carcinoma is referred to the malignant lesions of the pancreatic epithelial tumour. *Case report.* A 52-year-old female patient presented with pain in the umbilical and epigastric regions for 5 months and noticed a solid visible tumour on the left side of the abdomen 3 months ago when she lied down. The level of the CA125 was 47.64 U/ml (normal value <35 U/ml). Abdominal and pelvic magnetic resonance imaging (MRI) showed a cystic multiseptal mass in the left iliac region, defined as a left ovary tumour, while Computed tomography scan revealed a cystic tumour of the pancreatic tail. The patient underwent a resection of the pancreatic tail with a 20 cm cystic solid tumour, splenectomy and left hemicolectomy. Histopathology report confirmed mucinous cystic neoplasm of the pancreatic tail with associated invasive carcinoma (combined badly differentiated (G3) ductal (40%) and undifferentiated (G4) anaplastic (60%) carcinoma) pT1bN0. Postoperative course complicated with wound infection. The patient was discharged on postoperative day 10. The patient is still alive 2 years on follow-up. *Conclusions.* PMCN with associated invasive carcinomas are rare lesions of pancreas with relatively benign course. This malignant pancreatic tumour displays morphologies as pleomorphic epithelial cells and relatively mononuclear spindle cells, and not always tends to have underlying ovarian type stroma. The comprehensive histopathological examination of the tumour is necessary in order to cure most MCN patients with minimally invasive types.

**Key words:** pancreatic mucinous cystic neoplasm, IPMN, invasive carcinoma of the pancreas, pancreatic lesions, pancreatic cancer, mucinous cystic neoplasms, case report.

Received: 2023/02/20. Accepted: 2023/03/31.

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## Introduction

Pancreatic mucinous cystic neoplasm (PMCN) is a rare mucin producing cystic neoplasm that is histologically described by ovarian-type stroma [1]. This tumour is usually solitary and does not have a connection to the pancreatic ductal system. The incidence of PMCN is about 8% of all resected cystic lesions of the pancreas [2]. They are slow-growing, occur in the pancreatic duct epithelium, and predominantly affect women [3]. The PMCN is defined as mucinous cystic neoplasm (MCN) with an invasive carcinoma if the tumour has a contact with the pancreatic duct, or the tumour has mural nodularity and appears to be larger than 3 cm [4]. The prevalence of this form of tumour ranges from 6 to 55% of all mucinous cystic neoplasms [5]. Approximately 150 such cases have been reported in the literature so far [4]. Moreover, in our case the tumour is large in size with no underlying ovarian type stroma and rare TP53 mutation is present. Usually, this neoplasm is found in the body or tail of the pancreas of the middle-aged (perimenopausal) women (more than 98% of all cases) and rarely of the older man [4, 6]. The malignant form is associated with the age. It is more frequently found in older patients due to increased possibility of adenoma progression to carcinoma as the individual ages [4].

Here we present a case of PMCN with associated invasive combined G3 ductal and G4 anaplastic carcinoma (IDC), with no underlying ovarian type stroma.

## Case description

The patient has given their consent for the report. Approval from the Institutional Review Board was granted.

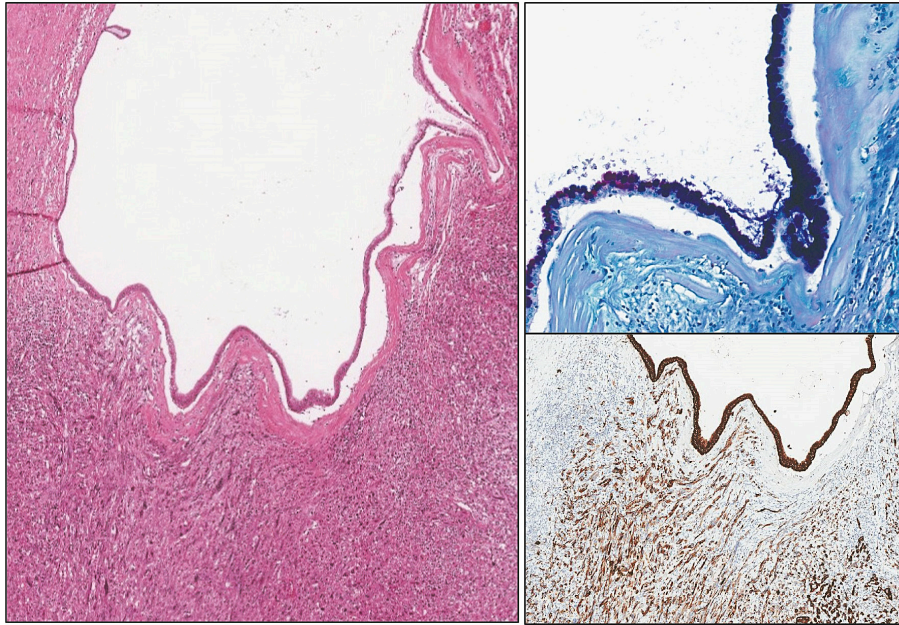
A 52-year-old female patient who complained about the pain in the umbilical and epigastric regions for 5 months presented to our clinic. Three months ago, she noticed a solid tumour on the left side of the abdomen when lying down.

The level of the CA125 was slightly increased – 47.64 U/ml (normal value <35 U/ml). Abdominal and pelvic magnetic resonance imaging (MRI) showed a cystic multiseptal mass in the left iliac region, defined as a left ovary tumour, while computed tomography (CT) scan of thorax, abdomen and pelvis revealed a cystic tumour of the pancreatic tail, cT3N0M0 – possibly a cystadenoma or cystadenocarcinoma.

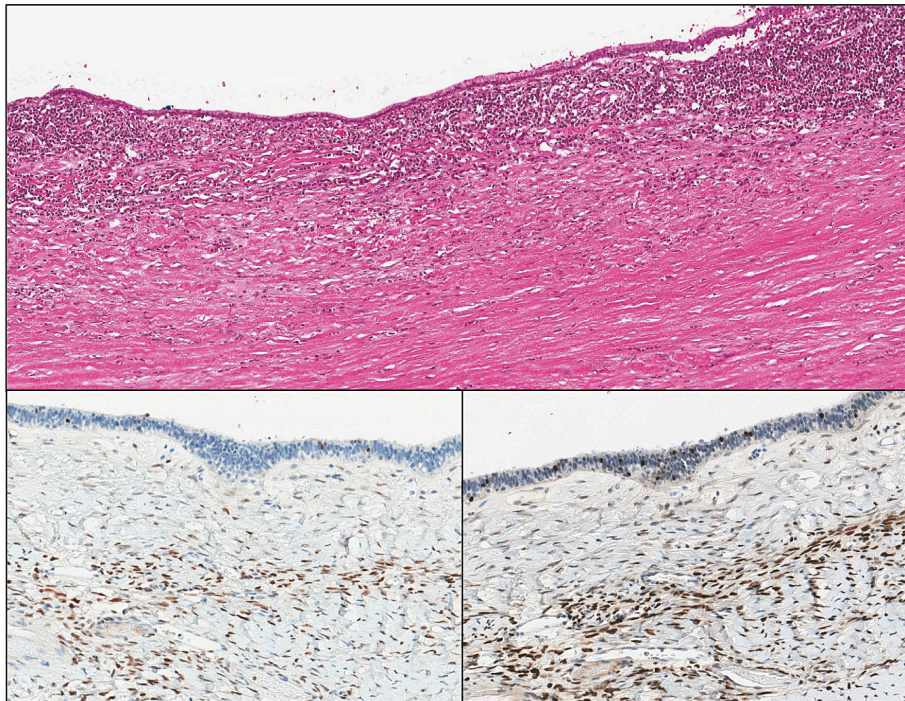


**Figure 1.** Multilocular cystic lesion with smooth inner surface, thick fleshy capsule and minimal haemorrhagic residue





**Figure 2.** At low power, a cyst lined by mucinous (AB/PAS on top right) epithelium overlying invasive component composed of pleomorphic spindle cells with strong pan-cytokeratin reaction (PanCK on bottom right)

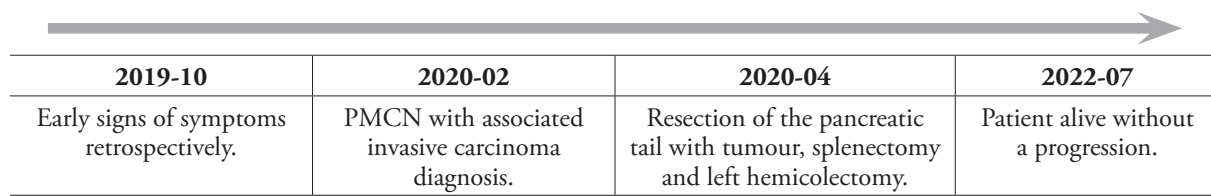


**Figure 3.** The ovarian type stroma of larger MCNs is often hyalinized and hypocellular, but stromal estrogen (bottom left) and progesterone receptors (bottom right) are present

The patient underwent a resection of the pancreatic tail with a 20 cm tumour, splenectomy and left hemicolectomy. Histopathology showed mucinous cystic neoplasm of the pancreatic tail with associated invasive carcinoma (combined poorly differentiated (G3) ductal (40%) and undifferentiated (G4) anaplastic (60%)

carcinoma) (Figure 1). It was staged as pT1bN0 considering that the maximum size of the identified invasive carcinoma was 8 mm and the 23 found regional lymph nodes were not involved (did not exceeded 8 mm). The intravascular invasion was not identified. The resection was R0. Microscopically pancreatic lesion was composed of a thick, hyalinized capsule surrounding mucin filled cystic cavity with peripheral septation and smaller secondary spaces. Inner surface of the cyst was lined with monomorphic PAS+ or AB+/PAS+ mucinous epithelium, focally exhibiting intraluminal micropapillarisation, nucleomegaly and stratification. An invasive component consisted of either irregular glandular structures (“ductal”) or solid sheets of eosinophilic pleomorphic spindle cells (“anaplastic”) was noted in a few slides (Figure 2). Invasive carcinoma had IN11 expression retained loss of SMAD4, strong diffuse nuclear positivity for p53 and was negative for Inhibin and CK5. The ovarian type stroma was not prominent (as it often is the case in large MCNs) but nuclear ER or PR positivity was unequivocal (Figure 3). Next-generation sequencing (NGS) identified PTPN11 and TP53 mutations.

Postoperative course complicated with wound infection. The antibiotics were administered according to bacteria culture test and the passive drainage with Penrose drains was applied. The patient was discharged on the 10<sup>th</sup> day after the operation. No further treatment was needed. She is still alive without a progression 27 months following the surgery (Figure 4).



**Figure 4.** Timeline of the presented case

## Discussion

Mucinous cystic neoplasm might progress to invasive form of the tumour. It occurs in up to a third of all cases (the frequency differs and depends on the study) and those are named as MCN with associated invasive carcinoma [4, 7]. There have only been about 150 such patients described in the literature but the number of patients with TP53 mutation and with no underlying ovarian type stroma (as in this case) is significantly lower [4]. IPMNs have a wide range of atypical grades, from low-grade dysplasia to aggressive malignancy [8, 9]. The likelihood of finding even small-sized IPMNs has increased due to recent advancements in radiologic imaging [10]. PMC's aetiology and pathophysiology are poorly understood. It is only clearly known that the mucin-producing cystic neoplasm histologically usually features the epithelium underlaid with ovarian-type stroma and is a precursor of the pancreatic ductal carcinoma [11]. However, a medullary phenotype was substantially related to SI, a wild-type KRAS gene, and a family history of any cancer in a first-degree relative in the study of Wilentz et al. [12]. Kryklyva et al described the first PMC case linked to a POLE mutation [13].

Patients with MCN can complain about abdominal pain. It is reported that for some patients it might start even in the right iliac fossa and radiate into the right lumbar region, while most of these patients admits left-sided, intermittent abdominal pain [14, 15]. Some patients can present with acute pancreatitis that could possibly result from pancreatic duct compression [16]. Some people with such diagnosis come to the hospital due to the lump in the left part of their abdomen [15, 17]. About quarter of the patients might appear asymptomatic, and the tumour might be detected at a regular health check-up [16, 18, 19]. In our case, the patient reported pain in the umbilical and epigastric regions and a solid visible tumour on the left side of the abdomen.



Laboratory tests are non-informative and normal range of cancer markers could not deny the diagnosis of pancreas cancer, therefore the main role in diagnostics takes visual investigations. In some reported cases an ultrasound-guided aspiration of the cystic fluid shows a normal [19] while in others a high level of CEA and CA19-9 [17]. However, CA19-9, the tumour marker of the pancreatic cancer, tends to be higher in invasive form compared to non-invasive form of the MCN [4]. Diagnostic tests mainly include abdominal and/or pelvic MRI and/or CT scan for visualisation of the tumour. MCN with invasive carcinoma should be at least 3 cm size, with the thicker cyst walls and while MCN is usually well circumscribed, malignant form is characterized by enhancing mural nodularity and calcification in the wall [4, 7]. The change of the pancreatic duct diameter with distal part of the pancreas atrophy is another feature found in an invasive form of the tumour. MRI tends to be more specific for interpreting internal components of this mass. In the majority of the reported cases, abdomen or/and pelvic CT was performed first followed by a more detailed diagnosis using the MRI scan [15, 18, 19]. Endoscopic ultrasound (EUS) can also be used for diagnostic as it better estimates the lesions and there is a possibility to take some fluid or cystic mural mass for histopathological investigation during the EUS [7]. Furthermore, positron emission tomography (PET) scan in some studies showed to be an accurate diagnostic test for differentiation of benign and malignant forms because it displayed hypermetabolic activity at the periphery of the mass [7, 15]. In addition to malignant IPMN, small-sized concurrent PDAC may also be detected using the ERCP with cytology [20]. The selection criteria for ERCP with cytology indication, however, are still not established. Therefore, routine ERCP for fluid or brush sampling in patients with IPMNs is not advised and should only be performed in research context [21]. In our case MRI and CT scan both were informative and none of the other visual investigations were performed. In most cases, the tumour is in the body and tail of the pancreas, while head of the pancreas remains unusual place for it to appear [22]. In this paper, the whole body CT scan revealed a cystic tumour of the pancreatic tail. At the first glance during the visual investigation, the malignant form of the tumour might be suspected because of the greater size of it. This piece of research suggests that MCN with and without an associated invasive carcinoma size significantly differs as 5.4 and 9.4 cm moderately [4]. In our case, the cystic mass was about 20 cm, so it could be expected to be malignant. The study [4] also refers that if intracystic papillary nodules are  $\geq 1$  cm they are highly associated with an invasive carcinoma.

In pathological investigation, MCN presents with ovarian-type stroma (OTS), which means spindle-shaped cells with scarce cytoplasm and round or elongated nucleus. If OTS is vague, then progesterone receptors (PR) immunohistochemical staining confirms MCN diagnosis. Its immunoreactivity is high and usually diffuses in low-grade dysplasia (LGD) or intermediate-grade dysplasia (IGD) but is weaker in high-grade dysplasia/carcinoma in situ (HGD/CIS). About 20% of all invasive forms might be a subset of undifferentiated/ sarcomatoid carcinoma and even have unusual osteoclast-like giant cells [4]. MCN with an invasive carcinoma has an expression of a high-molecular-weight transmembrane mucin (MUC1) that plays an important role in carcinogenesis and its positivity is related to poorer prognosis. Another feature that signs a worse prognosis is KRAS mutation in codon 12 or 13 [11]. This finding can also be identified in MCN, but the frequency of it might vary. For example, it is rarely reported in low-grade dysplasia of MCN [11]. In fact, a KRAS mutation is present in 60–80% of IPMN, as well as an overexpression of TP53 in 10–40% of high-grade IPMN and 40–60% of invasive carcinomas that have formed on IPMN [23]. During the histological examination, it is crucial to evaluate microscopic invasion and find out whether it is an early (T1a < 0.5 cm, T1b – 0.5 to 1 cm, T1c > 1 cm) or advanced (T2 or higher grade > 2 cm) invasion [4, 11]. Hui et al showed that patients with MCN with an invasive T1a or T1b carcinoma should be under continuous monitoring instead of receiving aggressive therapy [24]. Moreover, if invasive carcinoma is detected histopathologically as multifocal, it could be a sign to malignant behaviour of the tumour even if it is a small invasive carcinoma. In our case, a combined poorly differentiated (G3) ductal (40%) and undifferentiated (G4) anaplastic (60%) carcinoma with early (T1b) invasion was detected, and NGS identified PTPN11 and TP53 mutations.

The prognosis of MCNs after the radical surgery is excellent with the probability of five-year survival of 84–93% [4, 16, 25]. The patients with MCN with an invasive carcinoma have lower survival rates – about 26–63% [4, 7]. Metastatic lymph nodes are related to poor prognosis. Moreover, if MCN invades other organs, it usually affects ovaries and colon [4]. It is also found in our case – the tumour was infiltrating mesocolon of transvers colon and the greater omentum. However, the majority of patients with MCN with minimally invasive forms is cured, especially if the neoplasm is well investigated histopathologically [26].

## Conclusions

This piece of research confirmed that the mucinous cystic neoplasm of the pancreas with associated invasive carcinoma is a rare malignant pancreatic tumour, and typically displays several morphologies, including pleomorphic epithelial cells and relatively mononuclear spindle cells. However, most MCN patients with minimally invasive types are cured, particularly if the tumour is thoroughly examined histopathologically.

**Acknowledgements.** None.

**Declaration of interest statement.** The authors report there are no competing interests to declare.

**Data availability statement.** The data that support the findings of this study are available from the corresponding author, A. D., upon reasonable request.

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# ONKOLOGIJA

ISSN 1822-8623

## TAFINLAR + MEKINIST — adjuvantiniam III stadijos melanomos su BRAF V600 mutacija gydymui

TAFINLAR + MEKINIST – geriamasis taikinių terapijos vaistų derinys, skirtas metastatinės melanomos bei III stadijos adjuvantiniam melanomos gydymui po visiškos rezekcijos. Pacientui patvirtintais tyrimais turi būti įrodyta naviko su BRAF V600 mutacija diagnozė.<sup>1</sup>

Nacionalinis vėžio institutas  
Lietuvos onkologų draugija



Šaltiniai:  
1. TAFINLAR (dabrafenibaz). Preparato charakteristikų  
santrauka. <https://www.ema.europa.eu/en>; 2021-11-11.

**Valstinio preparato pavadinimas.** Mekinist 0,5 mg arba 2 mg pšviele dengtos tabletės. Kokybinė ir kiekybinė sudėtis. Tableteje yra atitinkami 0,5 mg arba 2 mg trametinibo. **Terapinės indikacijos.** Melanoma. **Terapinės indikacijos.** Melanoma. Trametinibas, vartojamas monoterapija ar derinyje su dabrafenibu, skirtas suaugusių pacientų, kuriems yra diagnozuota nerezekcinė arba metastazuojanti melanoma su BRAF V600 mutacija, gydymui. Kitą dieną trametinibo monoterapijai vartojamas pacientams, kurių liga progresavo po ankstesnio gydymo BRAF inhibitoriumi, neįrodyta. **Dozavimas ir vartojimo metodas.** Rekomenduojama trametinibo, vartojamo monoterapijai ar derinyje su dabrafenibu, dozė yra 2 mg per parą. Rekomenduojama kartu su trametinibu vartojamo dabrafenibo dozė yra 150 mg du kartus per parą. **Kontraindikacijos.** Padidėjęs jautrumas veikliajame arba bet kuriai pagalbiniai medžiagai. **Specialūs įspėjimai ir atsargumo priemonės.** Jei trametinibo vartojama derinyje su dabrafenibu, prieš gydymo pradžią reikia perskaityti dabrafenibo PCS. Sąveika su kitais vaistais. Vartojant dabrafenibo derinyje su trametinibu, gauta pradinė, apie savaitės trukmės sunkios nepageidaujamos odos reakcijos (SNOR), įskaitant Silveno-Olsonso sindromą, ir vėsiųjų preparatų reakciją su esančiomis bei sėtinėmis simptomais, kurie gali būti pavojingi gyvybei ar mirtini. Prieš pradedant gydymą, pacientus reikia informuoti apie sąveiką ir simptomus bei atidžiai stebėti odos reakcijas. Jei atsiranda simptomų, galinčių rodyti SNOR, dabrafenibo ir trametinibo vartojimą reikia nutraukti. Pacientams, vartojantiems trametinibo monoterapija ar derinyje su dabrafenibu, gali pasireikšti plaučių embolija ir gliučių vėjų trombozė. **Vaisingumas, nėštumo ir žindymo laikotarpis.** Vaisingo amžiaus pacientės turi būti informuotos, jog reikia naudoti veiksmingą kontracepciją netiesioginio trametinibo metu ir 16 savaičių po gydymo. Trametinibo turi būti nevartojama moterims nėštumo metu. Trametinibas gali sukurti žmogaus vaisingumą. **Nepageidaujamos poveikis.** Gydymas vien trametinibu. Labai dažnai: hipertenzija, kraujavimas, kosulys, dusulys, viduriavimas, pykinimas, vėmimas, vidurių užkietėjimas, pilvo skausmas, burnos džiūvimas, šibėrimas, [ ] spuogų panašūs šibėrimai, odos sausmė, nešėjimas, alopecija, nuovargis, periferinė edema, karščiavimas. Dažnai: šaltūnas, paronichija, celiulitas, pūlinėlis šibėrimas, anemija, jautrumo padidėjimas, dehidracija, neaiškūs matymai, vėgų edema, regėjimo sutrinkimas, kairiojo širdies funkcijos sutrinkimas, bradikardija, išstūmimo frakcijos sumažėjimas, limfiedema, pneumonitas, astenitas, eritema (raudoni) dėšų ir padų eritematosinis sindromas, odos irūrimas, odos skėlinėjimas, veslo edema, gliavinis uždegimas, silpnas. **Skirtingai trametinibo ir dabrafenibo derinį.** Labai dažnai: nasofaringitas, sumaišyti apšitas, galvos skausmas, pyragulys, hipertenzija, kraujavimas, kosulys, pilvo skausmas, vėmimas, vidurių užkietėjimas, vikturavimas, pykinimas, vėmimas, odos sausmė, nešėjimas, šibėrimas, eritema, artralgija, maišija, galūnių skausmas, nuorūnų spazmas, nuovargis, drebulys, astenija, periferinė edema, karščiavimas, [ ] gripo panašūs lpa. Dažnai: celiulitas, folikulitas, paronichija, pūlinėlis šibėrimas, odos plėčišgalinėis karcinoma, papiloma, sėborinėje karatozė, neutropenija, anemija, tromboticopopenija, leukopenija, dehidracija, hiponatremija, hipofosfatemija, hiperkalcemija, neaiškūs matymai, regėjimo sutrinkimas, uremia, širdies funkcijos sumažėjimas, hipotenzija, limfiedema, dusulys, burnos džiūvimas, stomatitas, [ ] akvė panašūs dermatitas, akcinė karatozė, neklinis prakaitavimas, hiperkeratozė, alopecija, dėšų ir padų eritematosinis sindromas, odos pažeidimas, hiperhidrozė, parūnas, odos irūrimas, jautrumas žvėms. **Registravimas.** Novartis European Limited, Artis, Pakuotė, 30 tablečių. Riboto išrašymo vaistinis preparatas. Teksto peržiūros data: 2021-11-11.

**Valstinio preparato pavadinimas.** Tafinlar 50 mg ir 75 mg kietosios kapsulės. Kokybinė ir kiekybinė sudėtis. **Kiekvienaje kapsulėje yra toks dabrafenibo molisato kiekis, kuris atitinka 50 mg arba 75 mg dabrafenibo.** **Terapinės indikacijos.** Melanoma. Trametinibas, vartojamas monoterapija ar derinyje su dabrafenibu, skirtas suaugusių pacientų, kuriems yra diagnozuota nerezekcinė arba metastazuojanti melanoma su BRAF V600 mutacija, gydymui. **Dozavimas ir vartojimo metodas.** Rekomenduojama dozė yra 150 mg dabrafenibo (vartojamo monoterapija ar derinyje su trametinibu) (po dvi 75 mg kapsules) du kartus per parą. **Kontraindikacijos.** Padidėjęs jautrumas veikliajame arba bet kuriai pagalbiniai medžiagai. **Specialūs įspėjimai ir atsargumo priemonės.** Jei dabrafenibo vartojama derinyje su trametinibu, prieš gydymo pradžią reikia perskaityti trametinibo PCS. Sąveika su kitais vaistais. **Vaisingumas, nėštumo ir žindymo laikotarpis.** Vaisingo amžiaus moterys turi naudoti veiksmingą kontracepciją metodu gydymo metu ir 2 savaites po dabrafenibo vartojimo nutraukimo ir praėjus 16 savaitėms po paskutinės trametinibo dozės, kai ja vartojamas derinys kartu su dabrafenibu. **Nepageidaujamos poveikis.** Gydymas vien dabrafenibu. Labai dažnai: papiloma, apšitos sumažėjimas, galvos skausmas, kosulys, pykinimas, vėmimas, viduriavimas, hiperkeratozė, alopecija, šibėrimas, dėšų ir padų eritematosinis sindromas, artralgija, maišija, galūnių skausmas, karščiavimas, nuovargis, drebulys, astenija. **Dažnai:** odos pūlinėlis šibėrimas, sėborinė karatozė, odos fibrocistinė papiloma, hipofosfatemija, hiperkalcemija, vidurių užkietėjimas, odos sausmė, nešėjimas, šibėrimas, eritema, artralgija, maišija, galūnių skausmas, nuorūnų spazmas, nuovargis, drebulys, astenija, periferinė edema, karščiavimas, [ ] gripo panašūs lpa. Dažnai: celiulitas, folikulitas, paronichija, pūlinėlis šibėrimas, odos plėčišgalinėis karcinoma, papiloma, sėborinėje karatozė, neutropenija, anemija, tromboticopopenija, leukopenija, dehidracija, hiponatremija, hipofosfatemija, hiperkalcemija, neaiškūs matymai, regėjimo sutrinkimas, uremia, širdies funkcijos sumažėjimas, hipotenzija, limfiedema, dusulys, burnos džiūvimas, stomatitas, [ ] akvė panašūs dermatitas, akcinė karatozė, neklinis prakaitavimas, hiperkeratozė, alopecija, dėšų ir padų eritematosinis sindromas, odos pažeidimas, hiperhidrozė, parūnas, odos irūrimas, jautrumas žvėms. **Registravimas.** Novartis European Limited, Artis, Pakuotė, 28 kapsulės. Riboto išrašymo vaistinis preparatas. Teksto peržiūros data: 2021-11-11. **Reklamos teksto parengimo data:** 2022-02-14.

Iliausi informacija apie šiuos vaistinius preparatus pateikiama Europos vaistų agentūros tinklalapyje <http://www.ema.europa.eu>.

Valstis registravimas atstovais: SIA Novartis Baltica Lietuvas Rialtas, Uptė g. 19, LT-08128 Vilnius. Specialūs patalpybė laikini pavėly ir (arba) gavo informacijos apie tai, turi prašyti Valstybinio vaistų kontrolės tarnyba prie Lietuvos Respublikos sveikatos apsaugos ministerijos el. paštu [NepageidaujamaR@vkt.lt](mailto:NepageidaujamaR@vkt.lt) ir kitu būdu, kaip nurodyta jos interneto svetainėje [www.vkt.lt](http://www.vkt.lt)

BS202117572 | 03/2022







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žurnalo INTERNISTAS priedas 2022 / 1 (30)

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# Storosios žarnos vėžio ankstyvosios diagnostikos programos atnaujinimo principai

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## Įvadas

Remiantis 2020 metų GLOBOCAN duomenimis, storosios ir tiesiosios žarnos vėžys (STŽV) pasaulyje tarp dažniausių piktybinių navikų užima trečią vietą pagal sergamumą ir antrą vietą pagal mirtingumą. 2020 metais buvo nustatyta daugiau nei 1,9 milijono naujų gaubtinės ir tiesiosios žarnos vėžio (įskaitant išangę) atvejų ir 935 000 mirčių. Apskaičiuota, kad būtent STŽV sudaro vieną iš dešimties atvejų, kai nustatomas vėžys, ir lemia vieną iš dešimties mirčių nuo onkologinės ligos [1]. Lietuvoje STŽV yra vienas dažniausių piktybinių navikų – 2020 metais jis diagnozuotas 1 892 asmenims, tai yra 11,4 proc. visų vėžio atvejų [2]. Lietuvoje STŽV užima trečią vietą pagal onkologinių ligų sukeltą naštą – tiek susijusią su dideliu mirštamumu, tiek su didele įtaka gyvenimo kokybei pasveikus [3].

Lietuvoje Storosios žarnos vėžio ankstyvosios diagnostikos programa buvo pradėta įgyvendinti 2009 metais Vilniuje ir Kaune. Nuo 2014 metų programa galėjo pasinaudoti visi Lietuvoje gyvenantys 50–74 metų žmonės. Šeimos gydytojai pasinaudoti programa, tai yra atlikti fekalijų imuninį tyrimą (FIT), kviečia patikros amžiaus sulaukusius asmenis. Neigiamas FIT rodo, kad pacientas yra sveikas. Tyrimas kartojamas po dvejų metų. Gavus teigiamą FIT, tiriamasis siunčiamas atlikti kolonoskopiją. Kolonoskopija (prireikus ir biopsija) leidžia objektyviai patvirtinti arba paneigti storosios žarnos vėžio diagnozę. Atliekant kolonoskopiją, gali būti taikoma bendroji nejautra. Nustačius polipus, juos reikėtų pašalinti ir atlikti histologinius tyrimus. Nenustačius pakitimų, pacientui FIT kartojamas po 10 metų.

1 lentelė. Storosios žarnos vėžio ankstyvosios diagnostikos programos Lietuvoje rodikliai

Rodiklis	Skaičius
FIT atlikta	1 899 266
FIT teigiami (proc.)	153 362 (8,08 proc.)
Atlikta kolonoskopija (procentais nuo teigiamų FIT)	87 950 (57,4 proc.)
Nustatyta adenomų (procentais nuo teigiamų FIT)	22 099 (14,4 proc.)
Adenomų nustatymo dažnis apiekant kolonoskopiją	25,1 proc.
STŽV (procentais nuo biopsijų)	1958 (6,2 proc.)
STŽV procentas nuo kolonoskopijų	2,2 proc.
STŽV procentas nuo teigiamų FIT	1,3 proc.
STŽV procentas nuo tikrintų asmenų	0,07 proc.
Dalyvavimas Storosios žarnos vėžio ankstyvosios diagnostikos programoje 2020 metais	–34 proc.

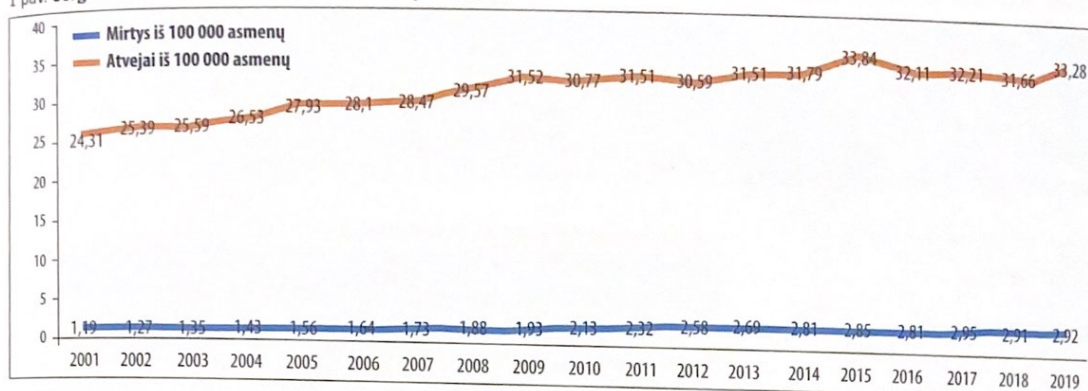
Programa finansuojama Valstybinės ligonių kasos lėšomis ir visi programos veiksmai tiriamiesiems yra nemokami. Programą prižiūri koordinavimo komitetas, kuriame dalyvauja Lietuvos Respublikos sveikatos apsaugos ministerijos, Valstybinės ligonių kasos, šeimos gydytojų, endoskopuotojų, patologų, chirurgų ir kitų specialybių bei pacientų atstovai [4].

Pagrindiniai Storosios žarnos vėžio ankstyvosios diagnostikos programos Lietuvoje rodikliai pateikti 1 lentelėje.

Dalyvavimas patikros programoje per 12 metų (2009–2020 metais) svyravo tarp 18 proc. ir 25 proc. per metus. Moterys programa naudojosi aktyviau. Nuo 2009 metų iki 2020 metų FIT atlikta 1 899 266 asmenims, kas sudaro apie 25 proc. tikslinės populiacijos (50–74 metų amžiaus gyventojų), kai keliamas tikslas yra ne mažiau nei 60 proc. FIT teigiamas buvo 7,1–10,2 proc. Kolonoskopija buvo padaroma 48–73 proc. asmenų (nors siekiamybė yra ne mažiau kaip 90 proc.), kuriems nustatytas teigiamas FIT. Tarp asmenų, kuriems buvo teigiamas FIT, 9,2–13,5 proc. buvo atliekama biopsija. Dažniausias radinys ištyrus biopsinę medžiagą – adenoma. STŽV buvo nustatomas 4,6–7,3 proc. biopsijų. STŽV nustatytas 0,93–1,3 proc. asmenų, kuriems buvo



1 pav. Sergamumo ir mirštamumo nuo STŽV Lietuvoje dinamika



teigiamas FIT, ir 0,07 proc. visų programoje dalyvavusių tiriamųjų.

1 pav. pateikta sergamumo ir mirštamumo nuo STŽV Lietuvoje dinamika, remiantis Higienos instituto ([www.hi.lt](http://www.hi.lt)) duomenimis. 2015 metais, kai visoje Lietuvoje buvo įdiegta Storosios žarnos vėžio ankstyvosios diagnostikos programa, buvo užfiksuotas didžiausias sergamumo rodiklis, o nuo 2017 metų mirštamumo dėl STŽV rodiklis nebedidėjo. Šie pokyčiai leidžia daryti prielaidą apie teigiamą patikros programos įtaką.

### Kaip pagerinti patikros programos efektyvumą?

Norint dar pagerinti Storosios žarnos vėžio ankstyvosios diagnostikos programos rezultatus, turėtų būti tobulinami toliau aptariamieji rodikliai.

Pirma, pakviestųjų asmenų procentas yra per mažas. Lietuva neturi centrinio patikrų registro ir aktyvios kvietimų sistemos, o tikslinės populiacijos asmenys šeimos gydytojų yra kviečiami dalyvauti atrankos programoje [5]. Atlikta metaanalizė patvirtino, kad žmonių dalyvavimas prevencinėse programose tiesiogiai priklauso nuo jų šeimos gydytojų suteikiamos informacijos apie vėžį ir patikros programas [6].

Kita problema yra ta, kad ne visiems asmenims, kuriems nustatytas teigiamas FIT, yra atliekama kolonoskopija. Pacientai, kurie nėra gerai informuoti apie prevencinę patikros programą, baiminasi galimų komplikacijų ir patiriamo diskomforto atliekant kolonoskopiją. Mažas atliekamų kolonoskopijų procentas galėtų būti siejamas ir su jau minėtos centrinės patikros registro ir aktyvių kvietimų sistemos neturėjimu Lietuvoje, kas apsunkina asmenų, kuriems nustatytas teigiamas FIT, suradimą ir kvietimą išsitiirti detaliau. Endoskopo puotojo pareiga yra kokybiškai atlikti kolonoskopiją. Yra keletas rodiklių, kurie lemia kokybiškai atliktą tyrimą. Remiantis Europos gaubtinės ir tiesiosios žarnos vėžio patikros ir diagnostikos kokybės užtikrinimo gairėmis, atliekant kolonoskopiją turėtų būti apžiūri-

ma storoji žarna iki distalinės klubinės žarnos apžiūra (jei nėra ryškios spindžio stenozės naviku ar kitų objektyvių priežasčių) [7]. Kitas matmuo, rodantis kokybišką gleivinės apžiūrą atliekant kolonoskopiją, yra adenomų nustatymo dažnis [8]. Net jei kolonoskopija yra atliekama kokybiškai ir nustatomi polipai, poliipektomija ne visada atliekama iš karto. Atlikus poliipektomiją, nėra aiškiai nurodyta tolesnė pacientų stebėjimo tvarka. Patvirtinus piktybinį darinį, nėra žinoma, kokie turėtų būti intervaliniai vėžio po skirtingų patikros etapų dažniai. Galiausiai patikros programos rezultatus galima vertinti tik remiantis finansinės atskaitomybės formomis, o ne standartizuotais medicininiais dokumentais.

Siekiant sumažinti mirtingumą ir sergamumą STŽV Lietuvoje, užtikrinti kokybišką patikros programos vykdymą, iškeltas tikslas atnaujinti ją. Storosios žarnos vėžio ankstyvosios diagnostikos programos efektyvumą užtikrina penki žingsniai:

- tiriamųjų sąrašo sudarymas;
- kvietimų išsiuntimas;
- atliktų FIT mėginių gavimas;
- asmenų, kuriems nustatytas teigiamas FIT, siuntimas atlikti kolonoskopiją;
- kolonoskopijos ir, jei reikia, biopsijos atlikimas.

### Tiriamųjų sąrašo sudarymas

Regioninis prevencinių programų koordinavimo centras (RPPKC), naudodamasis Gyventojų registrų centro duomenimis ir elektroninės sveikatos Onkologijos prevencijos posisteme (OPP), sudaro kviečiamųjų asmenų sąrašą ir įtraukia duomenis apie asmens amžių, lytį, gyvenamąją vietą ir apsilankymų duomenis asmens sveikatos priežiūros įstaigose. Sudarytame sąrašė kiekvienam tiriamajam priskiriamas kodas ir patikros programos numeris, pagal kuriuos bus identifikuojamas tiriamojo asmens mėginys. Siekiant išvengti klaidų, vokas, kvietimo laiškas, mėginys ir atgalinis



2 lentelė. Planuojami darbo krūviai patikros koordinavimo centrui

		Patikros koordinavimo centro darbas			FIT
			Gavimas	Pakartotiniai kvietimai	
Per metus	Kvietimų išsiuntimas	289018,5	202312,95	86705,55	202312,95
Per mėnesį	Kvietimų išsiuntimas	24084,88	16859,4125	7225,4625	16859,4125
Per dieną	Kvietimų išsiuntimas	1204,244	842,970625	361,273125	842,970625
Per valandą	Kvietimų išsiuntimas	150,5305	105,3713281	45,15914063	105,3713281

vokas pažymimi tuo pačiu brūkšniu kodu.

### Kvietimo siuntimas

Naudojant automatines adresų spausdinimo ir vokų klijavimo priemones, pagal priskirtą kodą laišakai paruošiami išsiųsti. Laiške turi būti nustatytos formos kvietimas dalyvauti tyrime, FIT mėginys ir vokas siuntimui atgal. Svarbu, kad kas 5 000 vokas būtų patikrinamas, ar sutampa kodas, patikros istorijos numeris ir asmens duomenys ant abiejų vokų, kvietimų ir mėginio. OPP fiksuojama tikrinimo data, tikrinimo rezultatas (sutampa / nesutampa). Atsiradus klaidai, turi būti stabdomas tolesnis vokų ir mėginių spausdinimas ir siuntimas, kol klaida yra ištaisoma.

### Mėginių gavimas

Gauti paštu mėginiai priimami RPPKC. Įsitikinama, kad atgalinio voko ir mėginio brūkšniniai kodai sutampa. Mėginys tiriamas automatiškai būdu, gaunamas atsakymas automatiškai, fiksuojamas OPP. Atsakymas tiriamajam generuojamas automatiškai. Neradus kraujo, nurodoma išvada *Normalaus tyrimo atsakymas*. Esant *Normalaus tyrimo atsakymui*, tiriamajam po dvejų metų siunčiamas naujas kvietimas, jeigu jis bus jaunesnis nei 75 metų ir viena diena. Radus kraujo, nurodoma išvada *Rastų pakitimų atsakymas*. Vadinasi, pacientui bus indikuotina kolonoskopija ir tolesnis ištyrimas. Jeigu RPPKC per vieną mėnesį negauna atgalinio laiško su tyrimo mėginiu, kuriamas pakartotinio kvietimo dalyvauti programoje laiškas ir tai pažymima OPP. Gavus laišką, kuriame nurodyta, kad adresatas nerastas, apie tai pažymima OPP.

### Siuntimas atlikti kolonoskopiją

Kvietimą atlikti kolonoskopiją gauna tik žmonės, kurių FIT teigiamas, atrinkti iš OPP susistemintų duomenų. Asmuo, gavęs kvietimą, turi kreiptis į šeimos gydytoją dėl siuntimo kolonoskopijos procedūrai. Kolonoskopijos paslauga atliekama OPP numatytu laiku ir vietoje. Data ir laikas gali būti keičiami. Ko-

3 lentelė. Planuojamas darbo krūvis šeimos gydytojui

Siuntimas atlikti kolonoskopiją	Gydytojui	Kolonoskopijos rezultato vertinimas gydytojui
Per metus	30547,326	15,27366285
Per mėnesį	2545,6105	1,272805238
Per dieną	127,28052	
Per valandą	15,910065	
Per minutę	0,2651678	

lonoskopijas atliekanti asmens sveikatos priežiūros įstaiga iš anksto (prieš keturias–septynias dienas) susisiekiama su pacientu ir patikslina, ar pacientas atvyks, primena reikalingą pasiruošimą kolonoskopijos procedūrai ir patikslina, ar pacientas turi šeimos gydytojo siuntimą.

### Kolonoskopijos ir biopsijos paslauga

Atliekant kolonoskopiją, rekomenduojama gili sedacija ar bendroji nejautra. Pacientui atsakius bendrosios anestezijos, kolonoskopija gali būti pradėdama ir be jos, tačiau būtina užtikrinti anesteziologo dalyvavimą. Atliekama nuodugni kolonoskopija, kurios metu turi būti atlikta aklosios žarnos ir distalinės klubinės žarnos apžiūra (jei nėra ryškios spindžio stenozės naviku ar kitų objektų priežasčių). Radus storosios žarnos patologinių pakitimų (navikas, polipas ar kt.), imama biopsinė medžiaga arba siunčiamas tirti pašalintas polipas. Nustatyti polipai turi būti šalinami iš karto, nebent jie yra >40 mm ar jų lokalizacija nėra patogi. Kolonoskopijos rezultatai fiksuojami OPP, paaiškinami pacientui ir jį lydintiems asmeniui. Pacientui atiduodamas atspausdintas kolonoskopijos aprašas.

### Planuojami patikros programos nuo STŽV poreikiai

Remiantis 2018 metų Lietuvoje vykdytos patikros programos duomenimis, pakvietus dalyvauti 60 proc. (578 037) asmenų, iš kurių dalyvautų 70 proc. (404 626), patikros koordinavimo centras turėtų išsiųsti vidutiniškai pusterčio kvietimo per minutę (2 lentelė), o šeimos gydytojui tektų konsultuoti vidutiniškai 1,27 paciento per mėnesį (3 lentelė).

Lentelėse pateikti kolonoskopijos poreikiai skirtingose apskrityse.



4 lentelė. Kolonoskopijos poreikiai Lietuvos apskrityse

Sąlygos: 60 proc. – kvietimai, 70 proc. – dalyvavimas, 95 proc. – siuntimas kolonoskopijai						
Pagal apskritis	Procentai	Gyventojai	Kolonoskopijų	Kolonoskopijos centrų	Endoskopoutojų max	Biopsinių tyrimų
Vilnius	26	250482,7	7 942	4	26	2 526
Kaunas	20	192679	6 109	3	20	1 943
Klaipėda	12	115607,4	3 666	2	12	1 166
Šiauliai	10	96339,5	3 055	2	10	972
Panevėžys	8	1536,32	2 444	1	8	777
Alytus	5	48169,75	1 527	1	5	486
Marijampolė	5	48169,75	1 527	1	5	486
Telšiai	5	48169,75	1 527	1	5	486
Tauragė	4	38535,8	1 222	1	4	389
Utena	5	48169,75	1 527	1	5	486
Sąlygos: 60 proc. – kvietimas, 50 proc. – dalyvavimas, 83 proc. – siuntimas kolonoskopijai						
Pagal apskritis	Procentai	Gyventojai	Kolonoskopijų	Kolonoskopijos centrų	Endoskopoutojų max	Biopsinių tyrimų
Vilnius	26	250482,7	4 061	2	14	1 519
Kaunas	20	192679	3 124	2	10	1 169
Klaipėda	12	115607,4	1 874	1	6	701
Šiauliai	10	96339,5	1 562	1	5	584
Panevėžys	8	1536,32	1 249	1	4	468
Alytus	5	48169,75	781	0	3	292
Marijampolė	5	48169,75	781	0	3	292
Telšiai	5	48169,75	781	0	3	292
Tauragė	4	38535,8	625	0	2	234
Utena	5	48169,75	781	0	3	292

2 pav. Storosios žarnos patikros programoje dalyvavusių asmenų dinamika



### Planuojama našta ir rezultatai tiriamiesiems

Pakvietus 60 proc. (578 037) pacientų, iš kurių dalyvautų 70 proc. (404 626), 2 proc. dalyvių būtų nustatomi pakitimai (adenomos ar vėžys) ir tik 0,04 proc. iš jų galėtų pasireikšti nepageidaujami reiškiniai atliekant kolonoskopiją (perforacija, kraujavimas, mirtis). Detalesni duomenys pateikiami 5 lentelėje.

Dinamikoje stebimas didėjantis pacientų įsitraukimas į Storosios žarnos vėžio ankstyvosios diagnostikos programą. Pavyzdžiui, 2019 metų duomenimis, storosios žarnos vėžio ankstyvosios diagnostikos finansavimo progra-

moje numatytas paslaugas gavo beveik 261 000 asmenų, tai yra apie 8 proc. daugiau nei 2018 metais (2018 metais – daugiau kaip 241 000 asmenų) [9].

Dėl didėjančio pacientų srauto programoje reikalingas ir didesnis finansavimas. Programos pradžioje finansavimas siekė 2,41 mln. eurų. Kiekvienais metais jis didėjo. 2020 metais patikros programai buvo skirta 4,36 mln. eurų, o 2022 metais – beveik 5,7 mln. eurų [10].

Patikros programos kokybės rodikliai būtų automatiškai stebimi OPP, kur 54 iš 135 stebimų kokybės kriterijų yra skirti būtent užtikrinti kolonoskopijos kokybę.



5 lentelė. Numatoma kolonoskopijos nauda ir našta tiriamiesiems

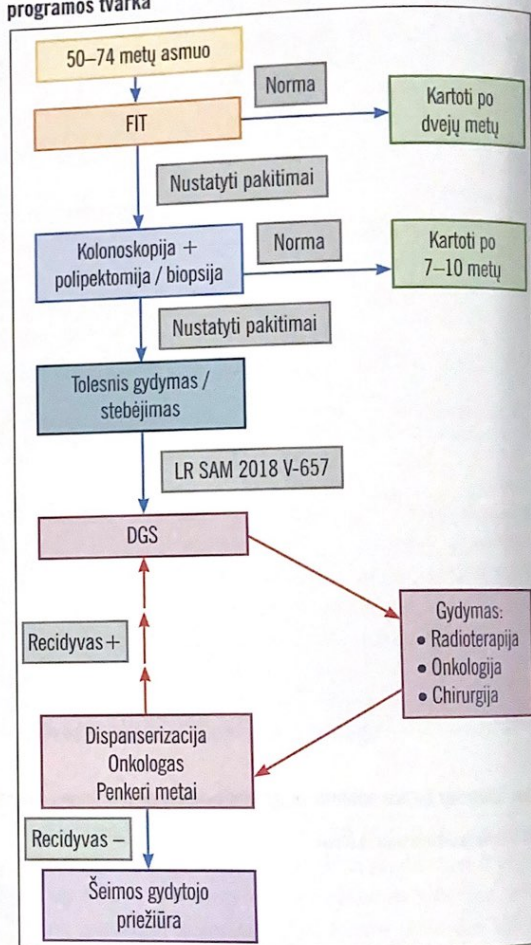
Nustatoma adenomų	7636,831
Nustatoma vėžio	458,2099
Įvyks perforacijų	9,164198
Dėl perforacijų mirs	1,37463
Įvyks kraujavimų	152,7366

Storosios žarnos vėžio ankstyvosios diagnostikos programos tvarką yra patvirtinusi Lietuvos Respublikos sveikatos apsaugos ministerija (3 pav.). Programoje gali dalyvauti 50–74 metų žmonės. Atlikus FIT ir nenustačius pakitimų, tyrimas kartojamas po dvejų metų. Nustačius pakitimų, pacientui paskiriama kolonoskopija. Kolonoskopu nenustačius pakitimų, tyrimas kartojamas po septynerių–dešimties metų. Radus pakitimų, daugiadalykė gydytojų komanda sprendžia dėl tolesnio paciento gydymo ar stebėjimo. Vėliau pacientą penkerius metus stebi gydytojas onkologas. Įvykus recidyvui, pacientas vėl konsultuojamas daugiadalykės gydytojų specialistų komandos. Ligai nesikartojant, pacientą stebi šeimos gydytojas.

Pažeidimų, nustatytų kolorektalinio vėžio atrankinės patikros metu, valdymas būtų vykdomas remiantis Lietuvos Respublikos sveikatos apsaugos ministerijos įsakymu Nr. V-657 *Dėl storosios (gaubtinės) žarnos piktybinio naviko, tiesiosios ir riestinės gaubtinės žarnos jungties piktybinio naviko ir tiesiosios žarnos piktybinio naviko diagnostikos ir gydymo tvarkos aprašo patvirtinimo*.

Patikros programos kokybei užtikrinti reikalinga tam pritaikyta informacinė sistema, kurios kūrimo grafikas nuo planuoto, deja, atsilieka.

3 pav. Storosios žarnos vėžio ankstyvosios diagnostikos programos tvarka



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