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Analiza krzywych uczenia resekcji pierwotnych złośliwych i przerzutowych guzów wątroby w aspekcie bezpieczeństwa pacjenta.

Learning curves analysis for resections of primary and metastatic liver malignancies in terms of patient's safety.

Praca doktorska

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Spis treści:

1. NOTA INFORMACYJNA

Niniejsza dysertacja doktorska składa się z monotematycznego cyklu trzech oryginalnych prac naukowych opublikowanych w recenzowanych czasopismach branżowych o zasięgu międzynarodowym. Wszystkie periodyki, w których ukazały się wyżej wymienione artykuły figurują na Liście Czasopism Naukowych Ministra Nauki i Edukacji[1], a dwa z nich również na Liście Filadelfijskiej[2].

Łączna liczba punktów Ministra Nauki i Edukacji uzyskana przez wyżej wymienione publikacje wynosi 300, a całkowity współczynnik oddziaływania (*Impact Factor*) 6,78 punktów.

Doktorant we wszystkich trzech pracach jest zarówno pierwszym, jak i korespondencyjnym autorem. Wniósł on znaczący wkład w powstanie wszystkich prac, w szczególności polegający na:

1. stworzeniu hipotez naukowych,
2. weryfikacji zgromadzonych danych pod względem przydatności w projekcie badawczym,
3. analizie statystycznej,
4. opracowaniu wyników,
5. prezentacji wniosków, oraz
6. napisaniu artykułów naukowych i przygotowaniu odpowiedzi na ich recenzje,

co zostało potwierdzone w załączonych oświadczeniach Współautorów publikacji.

Na przeprowadzenie projektu badawczego uzyskano zgodę Komisji Bioetycznej Uniwersytetu Jagiellońskiego nr 1072.6120.238.2021 z dnia 29 wrzesień 2021 (w załączniku).

[1] https://www.gov.pl/web/edukacja-i-nauka/ujednolicony-wykaz-czasopism-naukowych
[2] Journal Impact Factor - (impactfactorforjournal.com)

2. WPROWADZENIE

2.1 Pierwotne nowotwory złośliwe wątroby

Do najczęstszych pierwotnych nowotworów złośliwych wątroby zaliczamy raka watrobowokomórkowego (*hepatocellurar carcinoma; HCC*) oraz raka wewatrzwątrobowych przewodów żółciowych (*Intrahepaticcholangiocarcinoma; ICC*), które są klasyfikowane wg kodu C22 zgodnie z Międzynarodową Statystyczną Klasyfikacja Chorób i Problemów Zdrowotnych - zwykle używana jest skrócona nazwa Międzynarodowa Klasyfikacja Chorób (*International Statistical Classification of Diseases and Related Health Problems ; International Classification of Diseases , ICD*) [1].

Do uznanych czynników ryzyka raka wątrobowokomórkowego należą:

- przewlekła infekcja wirusem zapalenia wątroby typu B,
- przewlekła infekcja wirusem zapalenia wątroby typu C,
- długotrwała ekspozycja na alfa-toksynę B1,
- nadużywanie alkoholu,
- alkoholowa i niealkoholowa marskość wątroby,
- płeć męska,
- wiek > 60 roku życia,
- otyłość [2-4].

Rak wątrobowokomórkowy jest rozpoznawany częściej w populacjach rozwiniętych w porównaniu do krajów rozwijających się, a szczyt zapadalności przypada na siódmą dekadę życia [5,6]. Rak wewnątrzwątrobowych przewodów żółciowych również dominuje w krajach rozwiniętych, lecz szczyt zapadalności występuje w młodszym wieku – około pięćdziesiątego roku życia [7,8]. Zidentyfikowano następujące czynniki ryzyka raka wewnątrzwątrobowych przewodów żółciowych:

- kamica przewodów żółciowych – najsilniejszy czynnik ryzyka [9],
- kamica pęcherzyka żółciowego,

- przewlekłe stany zapalne wewnątrzwątrobowych przewodów żółciowych
- nikotynizm,
- płeć męska [9-11]

W roku 2019 wg Krajowego Rejestru Nowotworów w Polsce odnotowano 1463 przypadki pierwotnych nowotworów wątroby (886 wśród mężczyzn i 577 wśród kobiet), natomiast standaryzowany na populacje światową współczynnik zapadalności wyniósł 2,81 (odpowiednio 2,74 dla mężczyzn i 2,91 dla kobiet) [12]. W tym samym roku potwierdzono 2060 zgonów z powodu w/w nowotworów złośliwych (1191 wśród mężczyzn oraz 869 wśród kobiet), a współczynnik umieralności standaryzowany na populację świata wyniósł 5,37 (odpowiednio 6,41 dla mężczyzn i 4,39 dla kobiet) [12]. Już na podstawie wstępnej analizy danych epidemiologicznych dotyczących zapadalności i umieralności z powodu pierwotnych nowotworów złośliwych wątroby można stwierdzić, że charakteryzują się one niekorzystną prognozą co do całkowitego wyleczenia, a co za tym idzie wysoką śmiertelnością.

Badając trendy zarówno zapadalności jak i umieralności z powodu pierwotnych nowotworów wątroby w populacji polskiej wykazano obniżenie współczynnika zapadalności w latach 1998-2016 zarówno w populacji kobiet jak i mężczyzn [13]. Również w tym okresie stwierdzono malejący trend w umieralności zarówno kobiet jak i mężczyzn z powodu pierwotnych nowotworów wątroby w Polsce [13]

2.2 Przerzutowe nowotwory wątroby

Wątroba jest bardzo częstym miejscem lokalizacji przerzutów nowotworów złośliwych. Mogą one występować synchronicznie z pierwotnym ogniskiem nowotworu złośliwego, być rozpoznane w trakcie pierwotnej diagnostyki, i podwyższać stopień zaawansowania choroby nowotworowej, lub wystąpić w okresie po zakończonym leczeniu radykalnym – wtedy diagnozujemy przerzuty metachroniczne. Przyczyną ponad połowy wszystkich przerzutów do wątroby są nowotwory złośliwe przewodu pokarmowego, wśród nich najczęściej do wątroby przerzutuje rak jelita grubego [14-16]. Jest to nierozerwalnie związane z charakterystyką tworzenia przerzutów pierwotnych nowotworów złośliwych przewodu pokarmowego poprzez układ żyły wrotnej [15]. Według Wang i wsp. do najczęstszych ognisk lokalizujących się w wątrobie należą przerzuty nowotworów złośliwych (1) płuc – 25,9%, (2) jelita grubego – 21,4%, (3) trzustki – 19,6%, (4) żołądka – 4,6%, a w populacji żeńskiej (5) piersi – 9,2% oraz (6) narządu rodnego – 6,9% [14]. Najczęstszym nowotworem złośliwym narządu rodnego dającym przerzuty do wątroby jest rak jajnika. Należy zwrócić uwagę, że nawet u kilkunastu pacjentek z rakiem jajnika zajęcie wątroby jest diagnozowane w momencie postawienia pierwotnego rozpoznania, przy czym ogniska wątrobowe mają zwykle charakter powierzchownego nacieku wątroby i powinny być usunięte w ramach pierwotnej lub interwałowej operacji cytoredukcyjnej tak by u pacjentki leczonej chirurgicznie z powodu raka jajnika, uzyskać całkowity lub optymalny poziom resekcji wszystkich zmian nowotworowych obecnych nie tylko w miednicy mniejszej lecz w całej jamie brzusznej [17-19]. Jedynie takie postępowanie daje największe szanse na długotrwałe przeżycia całkowite i wolne od wznowy, a co za tym idzie na wyleczenie z choroby nowotworowej [19,20].

2.3 Metody leczenia pierwotnych złośliwych i przerzutowych nowotworów wątroby

Metodą z wyboru w leczeniu radyklanym zarówno pierwotnych nowotworów złośliwych wątroby, jak również ognisk przerzutowych, jest leczenie operacyjne [21-23]. W niniejszej pracy posłużono się anatomiczno-chirurgiczną klasyfikacją resekcji wątroby rekomendowaną przez Międzynarodowe Towarzystwo Chorób Wątroby, Trzustki i Dróg Żółciowych (*International Hepato-Pancreato-Biliary Association; IHPBA*) [24].

W przypadku, gdy rozpoznane ogniska w wątrobie nie kwalifikują się do resekcji chirurgicznej można wykonywać embolizację naczyń wątrobowych, zarówno tętniczych *(transarterial chemoembolization; TAE*), jak i żyły wrotnej (*portal vain embolication;* PVE) z użyciem różnego rodzaju materiałów embolizacyjnych jak: alkohol poliwinylowy, polimery akrylowe, pochodne żelatyny [25-27]. Możliwe jest również wykorzystanie chemioterapeutyków oraz czynników antyangiogennych lub inhibitorów kinaz tyrozynowych –

mówimy wtedy o chemioembolizacji lub radiofarmaceutyków – wtedy mamy do czynienia z radioembolizacją [28,29]. Do niszczenia wątrobowych ognisk przerzutowych, rzadziej ognisk złośliwych nowotworów pierwotnych wątroby, wykorzystywane są metody destrukcyjne z wykorzystaniem energii cieplnej. [30,31].

Rozwój radioterapii stereotaktycznej (*stereotactic radiotherapy; SRT*) jak również wykorzystanie metod modulacji intensywności wiązki (*intensity modulated radiation therapy; IMRT*) oraz sterowania obrazem (*image guided radiotherapy; IGRT*) pozwala obecnie z powodzeniem wykorzystywać teleradioterapię do leczenia zarówno pierwotnych nowotworów złośliwych wątroby, jak i zmian przerzutowych [32].

2.4 Metodologia analizy procesów uczenia się

Chirurgia wątroby i dróg żółciowych stanowi istotny element szkolenia chirurga tak ogólnego jak i onkologicznego. Zgodnie z aktualnymi programami specjalizacji lekarz specjalizujący się w chirurgii ogólnej powinien wykonać łącznie 20 operacji wątroby i dróg żółciowych w module podstawowym, natomiast lekarz specjalizujący się w chirurgii onkologicznej zobowiązany jest do wykonania co najmniej 60 samodzielnych operacji nowotworów złośliwych [33,34]. W przypadku ginekologii onkologicznej program specjalizacji obejmuje wyłącznie wykonanie łącznie 15 procedur radykalnej hysterektomii u pacjentek z rakiem jajnika, dodatkowo nie precyzując zakresu operacji [35]. Tak więc nie tylko opanowanie technik chirurgicznych i ich walidacja, ale również odpowiednia metodologia nauczania stanowią istotne składniki szkolenia chirurgicznego w różnych specjalizacjach zabiegowych.

Jednym ze sposobów oceny procesu nabierania danych umiejętności jest analiza krzywej uczenia się czyli analiza opanowania danej umiejętności lub wiedzy w funkcji czasu, jaki poświęciliśmy na jej zdobycie z wykorzystaniem metody skumulowanej sumy kontrolnej wykresów (*cumulative sum control chart, CUSUM*) [36-38]. Technika ta, po raz pierwszy opisana przez E. S. Page'a, była początkowo stosowana do monitorowania zarówno wyników jak i do identyfikacji obszarów wymagających poprawy w sektorze przemysłowym; następnie, pod koniec 1970 roku, została użyta do analizy krzywych uczenia się najpierw dla chirurgii, a następnie w pozostałych dziedzinach medycyny [39]. Obecnie metoda ta jest szeroko wykorzystywana do oceny charakteru nabierania umiejętności manualnych, które są jedną z podstaw uzyskania samodzielności w chirurgii [36-38,40-41].

2.5 Sposoby oceny bezpieczeństwa pacjenta w chirurgii

Organizacja systemu udzielania świadczeń zdrowotnych, wiedza i doświadczanie lekarza, a w przypadku chirurga również umiejętności zastosowania technik operacyjnych, mają bezpośredni wpływ na bezpieczeństwo pacjenta, definiowane jako ogół działań podejmowanych w celu uniknięcia i prewencji zdarzeń niepożądanych, występujących podczas procesu udzielania świadczeń zdrowotnych [42]. To również ocena, analiza i zarządzanie ryzykiem występującym dla pacjenta w systemie ochrony zdrowia [43]. Zdarzeniem niepożądanym nazywamy nie tylko powikłanie procesu terapeutyczne lecz każdą szkodę wywołaną w trakcie lub w efekcie leczenia nie związana z naturalnym przebiegiem choroby, stanem zdrowia pacjenta lub ryzyko jej wystąpienia [44-45]. W procedurach chirurgicznych najczęściej występującymi zdarzeniami niepożądanymi są powikłania okołooperacyjne oraz pooperacyjne zarówno wczesne, jak i późne. W roku 1992 Clavien i wsp. przedstawili usystematyzowaną klasyfikację powikłań chirurgicznych, która następnie w roku 2004 została zmodyfikowana przez Dindo i wsp. obecnie jest szeroko wykorzystywana jako Klasyfikacja Clavien-Dindo [46-48]. Wyróżnia ona pięć stopni powikłań operacyjnych. Stopień 1: obejmuje każde odstępstwo od normalnego przebiegu pooperacyjnego bez konieczności leczenia farmakologicznego lub innych interwencji, obejmuje również infekcje rany pooperacyjnej, dopuszcza stosowanie leków przeciwwymiotnych, znieczulających oraz przeciwgorączkowych i elektrolitów; Stopień 2: obejmuje farmakoterapię inną niż w stopniu 1 oraz transfuzje krwi i całkowite żywienie pozajelitowe; Stopień 3 to konieczność wykonania procedur chirurgicznych, endoskopowych lub radiologicznych również w znieczuleniu ogólnym (stopień 3b); Stopień 4 obejmuje stany zagrożenia życia, w tym niewydolność wielonarządową (stopień 4b); Stopień 5 powikłań to śmierć pacjenta. Klasyfikacja powikłań chirurgicznych wg. Clavien-Dindo jest obecnie szeroko wykorzystywana w praktyce klinicznej i badaniach naukowych [49-52].

3. STRESZCZENIE

Wprowadzenie. Do najczęstszych pierwotnych nowotworów złośliwych wątroby zaliczamy raka wątrobowokomórkowego (*Hepatocellurar carcinoma*; HCC) oraz raka wewnątrzwątrobowych dróg żółciowych (*Intrahepatic cholangiocarcinoma*; ICC), dominują one w krajach rozwiniętych i charakteryzują się złym rokowaniem. Wątroba, ze względu na bogate ukrwienie, jest również częstym miejscem przerzutów wielu nowotworów złośliwych, w tym piersi, jelita grubego, płuc oraz jajników. Wyróżniamy synchroniczne przerzuty do wątroby – występują w chwili rozpoznania podstawowej choroby nowotworowej, oraz przerzuty metachroniczne, rozpoznawane nawet do kilkudziesięciu lat po zakończeniu radykalnego leczenia pierwotnego nowotworu złośliwego. Podstawową metodą radyklanego leczenia zarówno pierwotnych nowotworów wątroby, jak i przerzutów nowotworowych jest ich resekcja chirurgiczna, która stanowi również integralną część szkolenia specjalizacyjnego zarówno z chirurgii ogólnej jak i onkologicznej. Coraz więcej operacji wątroby wykonuje się przy użyciu technik minimalnie inwazyjnych np. z dostępu laparoskopowego lub wykorzystując chirurgię robotyczną. Równocześnie w wielu badaniach potwierdziło zarówno korzystne wyniki terapeutyczne, jak również bezpieczeństwo tych metod, niemniej jednak szkolenie w zakresie chirurgii otwartej nadal pozostaje ważną kwestią w chirurgii ogólnej i jak również onkologicznej, dlatego w niniejszej dysertacji zaplanowano kompleksową analizę krzywych uczenia się dla otwartych resekcji wątroby wykonywanych w nowotworach złośliwych wątroby w odniesieniu do bezpieczeństwa pacjentów.

Cel badania. Do głównych punktów końcowych należała ocena krzywych uczenia dla: (1) czasu wykonania zabiegu operacyjnego, (2) śródoperacyjnej utraty krwi oraz (3) czasu pooperacyjnego pobytu w szpitalu u pacjentów poddawanych małym i dużym resekcjom wątroby. Drugorzędowymi punktami końcowymi było wystąpienie zarówno małych jak i ciężkich działań niepożądanych u pacjentów poddanych resekcji wątroby.

Materiał i metody.

Kryteria kwalifikacji do analizy i punkty końcowe.

Po uzyskaniu zgody Komisji Bioetycznej Uniwersytetu Jagiellońskiego przeprowadzono retrospektywną analizę zanonimizowanych danych pacjentów których wykonano laparotomię i resekcję guza wątroby z powodu pierwotnych nowotworów złośliwych wątroby lub przerzutów. Analizowano okres od 1 stycznia 2010 r. do 31 grudnia 2020 r., a wszyscy pacjenci zostali poddani zabiegowi chirurgicznemu wykonanemu przez tego samego chirurga lub – w przypadku pacjentek z rakiem jajnika – przez ten sam zespół operacyjny. Zastosowano następujące kryteria włączenia do analizy: (1) wiek co najmniej 18 lat, (2a) pierwotny rak wątrobowokomórkowy lub wewnątrzwątrobowy rak przewodów żółciowych potwierdzony histopatologicznie, alternatywnie (2b) przerzuty raka jelita grubego do wątroby potwierdzone w raportach histopatologicznych lub (2c) rozpoznanie raka jajnika w stadium IIIC zgodnie z klasyfikacją Międzynarodowej Federacji Ginekologii i Położnictwa (*Fédération internationale de gynécologie et d'obstétrique*; FIGO) potwierdzone pełnym raportem histopatologicznym oraz (3) brak wcześniejszych operacji wątroby. W oparciu o drugie kryterium w analizie końcowej wyodrębniono następujące trzy grupy pacjentów:

- Grupa 1: pacjenci z pierwotnym nowotworem złośliwym wątroby, u których wykonano wyłącznie prawostronne lub lewostronne hemihepatektomie;
- Grupa 2: Pacjenci z metachronicznymi przerzutami do wątroby raka jelita grubego, u których wykonywano zarówno segmentomię, bisegmentomię, jak również prawo- i lewostronne hemihepatektomie;
- Grupa 3: Kobiety z rakiem jajnika w stadium FIGO IIIC, w tym synchroniczne przerzuty / przerzut do wątroby, u których wykonywano wyłącznie klinową resekcję wątroby jako integralną część operacji cytoredukcyjnej.

Pacjenci z (1) niekompletną dokumentacją medyczną; oraz w Kohorcie 3 dodatkowo (2), którzy byli operowani przez zespól wielodyscyplinarny z udziałem chirurga lub urologa, oraz pacjentki (3) z nienabłonkowym nowotworem złośliwym jajników zostali wyłączeni z badania.

Bezpieczeństwo pacjentów.

Bezpieczeństwo pacjentów oceniano na podstawie wystąpienia zdarzeń niepożądanych, które zdefiniowano jako lekkie i ciężkie działania niepożądane. Lekkie działania niepożądane odpowiadały powikłaniom stopnia I–IIIa zgodnie z klasyfikacją Claviena-Dindo i obejmowały: (1) zakażenie rany; (2) przedłużony pobyt w szpitalu (>10 dni); oraz (3) krwiak niewymagający interwencji chirurgicznej. Ciężkie działania niepożądane odpowiadały powikłaniom w stopniu IIIb–V wg. klasyfikacji Clavien'a-Dindo i były następujące: (1) śmierć pacjenta; (2) przyjęcie na oddział intensywnej terapii; (3) reoperacja z powodu krwawienia dootrzewnowego; (4) rozejście rany pooperacyjnej wymagające ponownego zszycia w znieczuleniu ogólnym; (5) przetoka wątrobowo-żółciowa; a w Kohorcie 3 dodatkowo (6) niesczelność zespolenia jelita grubego; (7) uszkodzenie moczowodu; (8) przetoka pęcherzowo-pochwowa lub odbytniczo-pęcherzykowa.

Procedury chirurgiczne.

Procedury resekcji wątroby zostały sklasyfikowane zgodnie z anatomiczno-chirurgiczną klasyfikacją resekcji wątroby rekomendowaną przez Międzynarodowe Towarzystwo Chorób Wątroby, Trzustki i Dróg Żółciowych (*International Hepato-Pancreato-Biliary Association;* IHPBA). Segmentektomię, bisegmentektomię i resekcję klinową wątroby (wykonywane wyłącznie w Kohorcie 3) uznano za małe resekcje wątroby, podczas gdy prawa / lewa hemihepatektomia i prawą / lewą rozszerzona hemihepatektomia oraz dwa przypadki formalnych tylnych resekcji segmentów 6 i 7 (bisegmentomie) zostały sklasyfikowane jako duże resekcje wątroby.

Przebieg szkolenia chirurgicznego.

Polski system kształcenia lekarzy wyróżnia specjalizację w onkologii ginekologicznej, ale nie zapewnia specjalizacji w chirurgii wątrobowo-żółciowej. Dlatego 30 lat temu opracowano, a następnie zwalidowano i wdrożono autorski, bezpieczny program szkolenia w chirurgii wątroby dedykowany specjalistom z zakresu chirurgii ogólnej oraz onkologicznej. W przeciwieństwie do powyższego szkolenie z ginekologii onkologicznej jest w pełni sformalizowane –obowiązkowy jest udział w co najmniej 15 procedurach cytoredukcyjnych u pacjentek z rakiem jajnika w tym wykonanie 5 zabiegów jako operator.

Analiza statystyczna.

Do wykreślenia krzywych uczenia użyto metody skumulowanej sumy kontrolnej wykresów (*cumulative sum control chart,* CUSUM). Wskaźnik masy ciała (BMI) obliczono dzieląc masę ciała przez kwadrat wysokości ciała i przedstawiono go jako kg/m2. Analizowane dane przedstawiono jako średnią ± odchylenia standardowego (SD) lub jako mediana oraz rozstęp międzykwartylowy (IQR) w zależności od ich rozkładu, ocenianego testem Kołmogorow'a-Smirnov'a. Następnie badane zmienne porównano przy użyciu parametrycznego testu t-Studenta lub nieparametrycznego testu U - Manna-Whitneya. Do oceny danych kategorycznych zastosowano test chi-kwadrat. Wartość $p < 0,05$ uznano za statystycznie istotną, a wszystkie obliczenia zostały wykonywane przy użyciu oprogramowania do analizy danych STATISTICA, (TIBCO Software Inc. 2017, wersja 13.0, Palo Alto, Kalifornia, USA).

Wyniki. Do analizy zakwalifikowano łącznie wyniki 362 pacjentów: 82 (22,65%) przydzielono do Grupy 1, 158 (43,65%) do Grupy 2, a 122 (33,70%) do Grupy 3.

Grupa 1 (Pacjenci z pierwotnymi nowotworami złośliwymi wątroby).

Do tej grupy włączono 47 (57,32%) kobiet i 35 (42,68%) mężczyzn w średnim wieku 55,07 lat (±11,64) i ze średnim BMI 26,88 kg/m2 (±4,57). U 61 (74,39%) pacjentów zdiagnozowano raka wątrobowokomórkowego, a u 21 (25,61%) raka wewnątrzwątrobowych przewodów żółciowych. Pacjenci z rakiem wewnątrzwątrobowych przewodów żółciowych byli młodsi, wykazywali niższe BMI i wykazywali mniejszą częstość występowania marskości wątroby w porównaniu z pacjentami ze zdiagnozowanym rakiem wątrobowokomórkowym (odpowiednio: 53,05 lat ±12,21 *vs.* 60,95 lat ±7,32; p = 0,006; 22,26 kg/m^2 ±42,64 *vs.* 24,52 kg/m^2 ±3,44; p = 0,008; 50/61 (81,97%) *vs.* 9/21 (42,86%); p<0,001). W Grupie A mediana czasu zabiegu operacyjnego wynosiła 255 min. (IQR: 110), mediana śródoperacyjnej utraty krwi wynosiła 342 ml (IQR: 154), a mediana czasu pooperacyjnej hospitalizacji wynosiła 10 dni (IQR: 9). Nie stwierdzono istotnych różnic dla mediany czasu zabiegu operacyjnego (250 min. (IQR:105) *vs.* 290 min. (IQR:60); p=0,245) mediany objętości utraconej krwi (355 ml (IQR:310) *vs.* 340 ml (IQR:315); p=0,232) ani mediany czasu hospitalizacji po zabiegu (11 dni (IQR:9) *vs.* 6 dni (IQR:7); p=0,060) pomiędzy pacjentami z rozpoznaniem raka wątrobowokomórkowego a chorymi z rakiem wewnątrzwątrobowych dróg żółciowych. Na podstawie wykresów czasu zabiegu operacyjnego i śródoperacyjnej utraty krwi w analizie krzywej uczenia zidentyfikowała odpowiednio procedurę 29. i 30. jako punkty odcięcia dla uzyskania stabilizacji i powtarzalności w procesach zdobywania doświadczenia.

W Grupie 1 zaobserwowano 40 (48,78%) powikłań w stopniu I-IIIa oraz 28 (34,15%) powikłań IIIB-V stopnia zgodnie z klasyfikacją Clavien'a-Dindo. Nie stwierdzono istotnych różnic w częstości powikłań między pacjentami z rakiem wątrobowokomórkowym i rakiem wewnątrzwątrobowych przewodów żółciowych (powikłania w stopniu I-IIIa: 29/61 (45,31%) *vs.* 12/21 (57,14%); p=0,467 i powikłania w stopniu IIIb-V: 20/61 (32,79%) *vs.* 8/21 (38,10%); p=0,677). Analiza krzywych uczenia wykazała, że częstość występowania powikłań stopnia I-IIIa zgodnie z klasyfikacją Clavien-Dindo zmniejszyła się po 26. zabiegu, co było zgodne z czasem operacji i porównywalne ze śródoperacyjną utratą krwi. Stabilny spadek częstości występowania powikłań stopnia IIIb-V osiągnięto po 37. zabiegu – znacznie później w porównaniu do krzywych czasu zabiegu operacyjnego oraz śródoperacyjnej utraty krwi.

Grupa 2 (Pacjenci z przerzutami raka jelita grubego do wątroby).

Grupa 2 składała się ze 158 pacjentów: 76 (49,10%) mężczyzn i 82 (51,90%) kobiet w średnim wieku 57,60 lat (13,03 ±) i średnim BMI wynoszącym 26,88 kg/m^2. Mediana czasu od pierwotnej operacji jelita grubego wynosiła 45 miesięcy (IQR: 36). Łącznie 107 przypadków (67,73%) sklasyfikowano jako małe resekcje wątroby, a 51 (32,27%) jako główne resekcje wątroby zgodnie z terminologią Międzynarodowego Towarzystwa Chorób Wątroby, Trzustki i Dróg Żółciowych. W całej Grupie B mediana czasu zabiegu operacyjnego wyniosła 205 min. (IQR: 165), mediana objętości śródoperacyjnej utraty krwi wynosiła 330 ml (IQR: 540), a mediana pooperacyjnego pobytu w szpitalu wynosiła 6 dni (IQR: 3). Mediana czasu zabiegu operacyjnego oraz mediana pooperacyjnej hospitalizacji były istotnie dłuższe u pacjentów, u których wykonano duże resekcje wątroby w porównaniu z pacjentami poddawanymi małej resekcją wątroby (400 min. (IQR: 195) *vs.* 170 min. (IQR: 600); p<0,001 oraz 8 dni (IQR: 7) *vs.* 5 (IQR: 3); p = 0,016). Podobnie większą medianę śródoperacyjnej utraty krwi obserwowano u pacjentów poddanych dużym resekcjom wątroby w porównaniu z pacjentami, u których wykonywano małe resekcji wątroby (450 ml (IQR: 980) *vs.* 170 ml (IQR: 155); p<0,001). Analizując czas wykonania zabiegu operacyjnego zidentyfikowano procedurę nr 19 jako punkt graniczny uzyskania stabilnego i powtarzalnego doświadczenia chirurgicznego dla małych resekcji wątroby, podczas gdy w przypadkach dużych resekcji wątroby punkt ten odpowiadał procedurze nr 28. Biorąc pod uwagę śródoperacyjną utratę krwi, punkty odcięcia krzywej uczenia się były następujące: procedura nr 17 dla małych i nr 24 dla dużych resekcji wątroby.

W całej grupie wystąpiło 71 (44,94%) powikłań w stopniach I-IIIa oraz 28 (17,72%) powikłań w stopniach iiiB-V stopnia z klasyfikacją Claviena-Dindo. Wykazano nieistotne różnice w liczbie powikłań w stopniach I-IIIa oraz IIIb-V między pacjentami poddanymi małym resekcjomw porównaniu do pacjentów, u których wykonano duże resekcje wątroby (46 (42,99%) *vs.* 25 (49,02%); p = 0,476 oraz 15 (14,02%) *vs.* 13 (25,49%); p = 0,077). Ponadto analiza krzywych uczenia wykazała, że w przypadku procedur małych resekcji wątroby częstość występowania powikłań w stopniach I-IIIa zmniejszyła się po 19. zabiegu, jednak stabilny spadek powikłań w stopniach IIIb-V wg. klasyfikacji Clavien'a-Dindo został osiągnięty po 61. zabiegu, W przypadku procedur dużych resekcji wątroby powikłania w stopniach I-IIIa ustabilizowały się po 29. zabiegu, a stabilizację liczby powikłań w stopniach IIIb-V obserwowano po 39. zabiegu.

Grupa 3 (Kobiety z rakiem jajnika w stadium IIIC FIGO, w tym synchroniczne przerzuty do wątroby).

W ogólnej liczbie 122 kobiet kwalifikujących się do badania u 22 (18,03%) pacjentek potwierdzono podczas operacji cytoredukcyjnej obecność nacieku lub nacieków nowotworowych obejmujących wątrobę wykonując jednoczasowo klinową resekcję ognisk nowotworowych w wątrobie – pacjentki te zostały wyodrębnione do Grupy 3-A, podczas gdy Grupa 3-B obejmowała 100 (81,97%) kobiet, które nie wymagały takich procedur. W całej Grupie 3 mediana czasu zabiegu operacyjnego wynosiła 345,00 min (IQR: 195,50), mediana śródoperacyjnej utraty krwi wynosiła 2120,00 ml (IQR: 1422,50), a mediana czasu pooperacyjnej hospitalizacji 11,00 dni (IQR: 7,00). Nie stwierdzono również istotnych różnic między grupami 3-A i 3-B w medianie czasie trwania zabiegu operacyjnego (360,00 min. (IQR: 205,00) *vs.* 330,00 min. (IQR: 195,00); p=0,287), medianie śródoperacyjnej utraty krwi (1805,00 ml (IQR: 1660,00) *vs.* 2135,00 ml (IQR: 1275,00); p=0,279) ani też medianie czasu pooperacyjnego pobytu w szpitalu (10,00 (IQR: 2,50) *vs.* 11,00 (IQR: 8,00); p=0,194). W grupie 3-A analiza krzywych uczenia wykazała, Iż zabieg nr 10 był punktem odcięcia do uzyskania stabilizacji i powtarzalności czasu zabiegu operacyjnego; w grupie 3-B punkt ten został ustalony na procedurze nr 56. Podobnie podczas analizy całej kohorty, to właśnie procedura nr 53 została zidentyfikowana jako punkt odcięcia stabilnego i powtarzalnego czasu operacji. Śródoperacyjna analiza utraty krwi obu grup pozwoliła zidentyfikować przypadki nr 10 i nr 53 jako punkty odcięcia stabilizacji procedur chirurgicznych. W całej Grupie 3 stabilizację śródoperacyjnej utraty krwi osiągnięto na procedurze nr 62.

W Grupie 3 powikłania w stopniach stopnia I-IIIa stwierdzono u 62 (51,66%), a powikłania w stopniach IIIb-V u 42 (35,00%) pacjentek. Nie stwierdzono istotnych różnic w częstości występowania powikłań w stopniach I-IIIa oraz IIIb-V między grupą 3-A i grupą 3-B (9 (41,00%) *vs.* 53 (54,08%); p = 0,777 oraz 8 (36,36%) *vs.* 34 (34,69%); p = 0,882). Ponadto analiza krzywych uczenia dotycząca powikłań chirurgicznych wykazała, że w całej Grupie 3 częstość występowania powikłań w stopniach I-IIIa ustabilizowała się po 53. procedurze, natomiast stabilny spadek powikłań w stopniach IIIb-V wg. klasyfikacji Clavien'a-Dindo osiągnięto po 61. zabiegu. Stabilizację powikłań w stopniach I-IIIa oraz IIIb-V uzyskano odpowiednio z 12. i 47. zabiegiem dla Grupy 3-A, podczas gdy w Grupie 3-B ustabilizowały się one po 17. i 56. procedurze.

Wnioski.

1. W otwartych hemihepatektomiach czas zabiegu operacyjnego oraz śródoperacyjna utrata krwi nie mogą być predyktorami powikłań w stopniach IIIb-V zgodnie z klasyfikacją Clavien'a-Dindo.

2. Krzywe uczenia się dla dużych resekcji wątroby z powodu guzów przerzutowych są podobne do krzywych uczenia się hemihepatektomii wykonywanych w pierwotnych nowotworach złośliwych wątroby, dlatego rodzaj i charakter guza wątroby (pierwotny lub przerzutowy) nie wydaje się wpływać na krzywą uczenia się.

3. Zgodnie z oczekiwaniami, małe resekcje wątroby wykonywano szybciej i z mniejszym poziomem śródoperacyjnej utraty krwi, z krótszymi pobytami pooperacyjnymi i mniejszą liczbą powikłań zgodnie z klasyfikacją Clavien'a−Dindo w porównaniu z dużymi resekcjami wątroby.

4. Potrzeba było mniej procedur, aby uzyskać stabilizację i powtarzalność czasu operacyjnego i śródoperacyjnej utraty krwi w małych resekcjach wątroby w porównaniu z dużymi resekcjami wątroby.

5. Klinowa resekcja wątroby jako integralna składowa chirurgii cytoredukcyjnej u kobiet z zaawansowanym rakiem jajnika może być bezpiecznie wykonywana przez ginekologów onkologów.

6. Dodatkowo klinowa resekcja wątroby wykonywana przez ginekologa onkologa w ramach operacji cytoredukcyjnej nie zwiększa ryzyka powikłań, nie wpływa istotnie na czas zabiegu operacyjnego, ani śródoperacyjną utratę krwi jak również czas pooperacyjnej hospitalizacji.

4. ABSTARCT

Background. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two most common primary malignant liver cancers affecting mostly developing populations and presenting poor prognoses. Additionally, liver is a critical organ and a common metastatic site of many malignancies, including breast, colorectal, lung, and ovarian. These metastases can be recognized synchronously with primary tumour diagnoses or can occur up to decades after the primary radical treatment completion. Liver resections have become the first-line treatment for primary and metastatic tumours and, therefore, are considered a core aspect of surgical training. More and more of liver surgeries are performed using minimally invasive techniques such as e.g. laparoscopic and robotic approaches, and a significant amount of research confirmed both the feasibility and safety of those methods. Nevertheless, open surgery still remains an important element of general and oncologic surgery residency training, and therefore, we intended to investigate the learning curves for open surgery in liver malignancies in relation to patients' safety.

Aim. Learning curves for (1) operating time; (2) intraoperative blood loss; and (3) postoperative hospital stay duration in patients undergoing small and major liver resections were the primary endpoints. The secondary endpoints were incidences of minor and severe adverse effects of liver resections.

Material and Methods.

Eligibility of the study and endpoints.

A retrospective analysis of the medical registry comprising patients who underwent laparotomy and liver tumour resection due to primary liver malignancies or metastases was approved by the Institutional Review Board. The study covered the period from 01 January 2010 until 31 December 2020, and all patients included received surgery performed by the same surgeon or, in case of the women with ovarian cancer, the same operating team. The

inclusion criteria were as follows: (1) age 18 years or above; (2) no previous liver surgeries; and (3a) primary HCC or ICC in histopathological reports or (3b) liver metastases of colorectal cancer confirmed in histopathological reports or (3c) full histopathological report confirming ovarian cancer diagnosis at stage IIIC according to the International Federation of Gynaecology and Obstetrics (FIGO) classification. Based on the above criteria, the following three patient cohorts were distinguished for final analyses:

- Cohort 1: patients with a primary liver malignancy, undergoing left / right hemihepatectomies;
- Cohort 2: patients with metachronous liver metastases of colorectal cancer, undergoing segmentomies, bisegmentomies and left / right hemihepatectomies where required;
- Cohort 3: women with FIGO stage IIIC ovarian cancer including synchronous liver metastases, undergoing solely liver wedge resections.

Patients (1) with incomplete medical records; or, as it was the case in Cohort 3, (2) who had surgery co-performed by a colorectal, oncologic, hepatobiliary surgeon or a urologist; or (3) with a non-epithelioid ovarian malignancy were excluded from the study. The primary endpoints analysed were as follows: (1) operating time measured from skin incision to skin closure; (2) intraoperative blood loss level, defined as blood volume removed by suction; and (3) postoperative hospital stay length from the first postoperative day to hospital discharge date. Secondary endpoints determine the performed procedures' safety.

Patient safety factors.

Patient safety was evaluated based on the presence of adverse events, an inevitable aspect of the medical services provided, and these events were defined either as minor adverse effects or severe adverse effects. Minor adverse effects matched complications type I–IIIa according to the Clavien−Dindo classification and included: (1) wound infection; (2) prolonged hospital stay (>10 days); and (3) nonsurgically managed hematoma. Severe adverse effects corresponded with the Clavien−Dindo IIIb–V complications and were as follows: (1) patient death; (2) admission to the intensive care unit; (3) reoperation due to intraperitoneal bleeding; (4) wound dehiscence requiring re-suturing under general anaesthesia; (5) hepatobiliary fistula; and additionally in Cohort 3, (6) leakage of rectosigmoid colon anastomosis; (7) ureteral leakage; (8) vesico-vaginal and recto-vesical fistula.

Surgical procedures type.

Liver resection procedures were classified according to the Brisbane 2000 Terminology of Liver Anatomy and Resections. Segmentectomies, bisegmentectomies and liver wedge resections (performed exclusively in Cohort 3) were considered small liver resections, while right / left hemihepatectomies and right / left extended hemihepatectomies as well as two cases of formal posterior segments 6 and 7 resections (bisegmentomies) were classified as major liver resections.

Basic characteristics of surgical training.

Although the Polish surgical training system distinguishes a specialisation in gynaecologic oncology, it does not provide a specialisation in hepatobiliary surgery. That is why 30 years ago, our tertiary surgery unit established and then developed a proprietary tutoring program in that procedure. Currently, the program is dedicated to specialists in general, colorectal and oncologic surgery. At present, one surgeon is training at a time, and starts operating only after finishing the theoretical tutorial and assisting in at least 20 hepatobiliary procedures. Such a procedure is safe for the patient, and it also allows the surgeons in training to develop their own competences and gain experience.

Contrary to the above, the training in gynaecologic oncology is well-established and formalised – during one’s residency, it is mandatory to perform at least 15 cytoreductive procedures in ovarian cancer patients under direct supervision, including 5 as the leading surgeon. In Cohort C, therefore, the monodisciplinary surgical team consisted of two gynaecologic oncologists who performed cytoreductive surgery during the whole study period. The third member of the surgical team was under training in obstetrics and gynaecology, and rotated according to their residency program.

Statistical Analysis.

The cumulative sum control chart (CUSUM) analysis was used to investigate the learning curve in terms of operative time, intraoperative blood loss level and the length of hospital stay, as well as incidences of minor and severe adverse effects. Body mass index (BMI) was calculated by dividing the body mass by the square of the body height and is presented as kg/m2. Data are presented as the mean ± standard deviation (SD)or as the median and interquartile range (IQR) depending on their distributions,

which were checked using the Kologomorov–Smirnov test. Then, the study groups were compared using the parametric Student's t-test and the nonparametric Mann–Whitney U test as appropriate. For evaluating categorical data, the chi-squared test was employed. A p value < 0.05 was considered statistically significant, and all the calculations were performed using STATISTICA data analysis software (TIBCO Software Inc. 2017, version 13.0, Palo Alto, CA, USA).

Results. In total, 362 cases were eligible for analysis: 82 (22.65%) were assigned to Cohort 1, 158 (43.65%) to Cohort 2 and 122 (33.70%) to Cohort 3.

Cohort 1 (Patients with a primary liver malignancy)

The study group comprised 82 patients: 47 (57.32%) females and 35 (42.68%) males with a mean age of 55.07 years (±11,64) and a mean BMI of 26.88 kg/m2 (±4.57). 61 (74.39%) patients were diagnosed with HCC, while 21 (25.61%) with ICC. Patients suffering from ICC were significantly younger, with a lower BMI and showed a lower prevalence of liver cirrhosis compared to patients diagnosed with HCC (respectively, 53.05 years ±12.21 *vs.* 60.95 years ±7.32; p=0.006; 22.26 kg/m^2±42.64 *vs.* 24.52 kg/m^2 ±3.44; p=0.008; 50/61 (81.97%) *vs.* 9/21 (42.86%); p<0.001). In the whole cohort, the median operating time was 255 min. (IQR: 110), the median intraoperative blood was 342 mL (IQR: 154), and median postoperative hospital stay was 10 days (IQR: 9). There were no significant differences between patients with HCC and ICC concerning the variables presented (250 min. (IQR:105) *vs.* 290 min. (IQR:60); 0.245

and 355 mL (IQR:310) *vs*. 340 mL (IQR:315); 0.232 and 11 days (IQR:9) *vs.* 6 days (IQR:7); p=0.060). Based on operating time and the intraoperative blood loss, the CUSUM analysis identified procedures no. 29 and 30, respectively, as the cut-off points of gaining stable and repeatable surgical experience.

In the entire cohort, 40 (48.78%) grade I-IIIa and 28 (34.15%) grade IIIB-V complications according to the Clavien−Dindo classification occurred, and there were no significant differences between HCC and ICC patients in complication rates (grade I-IIIa: 29/61 (45.31%) *vs.* 12/21 (57.14%); p=0,467 and grade IIIb-V: 20/61 (32.79%) *vs.* 8/21 (38.10%); p=0.677). The CUSUM analysis showed that the incidence of grade I-IIIa complications according to the Clavien−Dindo classification decreased after the 26th procedure, which was consistent with the operative time and comparable intraoperative blood loss levels. A stable decrease in the incidence of grade IIIb-V complications was accomplished after the 37th procedure, which was significantly higher than the operative time and intraoperative blood loss peak points.

<u>Cohort 2 (Patients with metachronous liver metastases of colorectal cancer)</u>

Cohort 2 comprised 158 patients: 76 (49.10%) males and 82 (51.90%) females of a mean age of 57.60 years (±13.03) and a mean BMI of 26.88 kg/m2. The median time from primary colorectal surgery was 45 months (IQR: 36). A total of 107 cases (67.73%) were classified as small liver resections and 51 (32.27%) as major liver resections according to the Brisbane 2000 terminology. In the entire group, the median operating time was 205 min. (IQR: 165), the median intraoperative blood was 330 mL (IQR: 540), and median postoperative hospital stay was 6 days (IQR: 3). The median operating time and median postoperative hospital stay were significantly longer in patients with major liver resections compared to patients undergoing small liver resection (400 min. (IQR: 195) *vs*. 170 min. (IQR: 600); p<0.001 and 8 days (IQR: 7) *vs.* 5 (IQR: 3); p=0.016). Similarly higher median intraoperative blood loss was observed in patients with major liver resections compared to patients undergoing small liver resection (450 mL (IQR: 980) *vs.* 170 mL (IQR: 155); p<0.001).

Based on operating time, the CUSUM analysis identified procedure no. 19 as the cut-off point of gaining a stable and repeatable surgical experience in patients with small liver resections, while in major liver resection cases, this point was established at procedure no. 28. When taking the intraoperative blood loss level into consideration, the cut-off points for the learning curve were following: procedure no. 17 for small and no. 24 for major liver resections.

In the entire cohort, 71 (44.94%) grade I-IIIa and 28 (17.72%) grade IIIB-V complications according to the Clavien−Dindo classification occurred. Some insignificant differences were reported in the number of both grade I-IIIa and grade IIIb-V complications between the small and major liver resections (46 (42.99%) *vs.* 25 (49.02%); p= 0.476 and 15 (14.02%) *vs.* 13 (25.49%); p=0.77). Furthermore, the CUSUM analysis showed that in the small liver resections cohort, the incidence of grade I-IIIa complications decreased after the 19th procedure, however, a stable decrease in grade IIIb-V complications was accomplished after the 61st procedure, which was significantly higher than the operative time and intraoperative blood loss peak points. In the major liver resections group, the prevalence grade I-IIIa complications stabilized after the 29th procedure, and stabilization of grade IIIb-V complications was observed after the 39th procedure.

Cohort 3 (Women with FIGO stage IIIC ovarian cancer including synchronous liver metastases)

Out of the total number of 122 women eligible for the study, we confirmed 22 (18.03%) patients with liver wage resection during the debulking surgery, and these were included in Group 3-A. Group 3-B comprised 100 (81.97%) women who did not require this procedure. In the entire cohort, the median operating time was 345.00 min (IQR: 195.50), the median intraoperative blood loss was 2120.00 mL (IQR: 1422.50) and the median hospital stay was 11.00 days (IQR: 7.00). There were no significant differences between groups 3-A and 3-B in the median operating time (360.00 min. (IQR: 205.00) *vs.* 330.00 min. (IQR: 195.00); p=0.287), median intraoperative blood loss (1805.00 mL (IQR: 1660.00) *vs.* 2135.00 mL (IQR: 1275.00); p=0.279) or postoperative hospital stay (10.00 (IQR: 2.50) *vs.* 11.00 (IQR: 8.00); p=0.194). In

Group 3-A, the CUSUM analysis of operating time indicated that procedure no. 10 was the cut-off point of gaining a stable and repeatable surgical experience; in Group 3-B, this point was established at procedure no. 56. Similarly, when the entire cohort was analysed, it was procedure no. 53 which was identified as the cut-off point of attaining a stable and repeatable operating time. The intraoperative blood loss analysis of both groups allowed us to identify cases no. 10 and no. 53 as the cut-off points of procedure stabilization. In the entire cohort, the stabilization of intraoperative blood loss was achieved at procedure no. 62.

When it comes to the incidence rate of grade I-IIIa and IIIb-V complications, there were 62 (51.66%) and 42 (35.00%) cases, respectively, in the entire cohort. There were no significant differences in the incidence of grade I-IIIa and IIIb-V complications between Group A and Group B (9 (41.00%) *vs.* 53 (54.08%); p=0.777 and 8 (36.36%) vs. 34 (34.69%); p=0.882). Furthermore, the CUSUM analysis of surgical complications showed that in the entire cohort, the incidence of grade I-IIIa complications stabilized after 53rd, and a stable decrease in grade IIIb-V complications was accomplished after the 61st procedure. For Group 3-A, the stabilization of grade I-IIIa and IIIb-V complications was gained with the 12th and 47th procedure, respectively, while in Group 3-B, they stabilized with the 17th and 56th procedure.

Conclusions.

1. In open hemihepatectomies, the operative time and intraoperative blood loss cannot be considered as surrogates for grade IIIb-V complications according to the Clavien−Dindo classification, as they present significantly different learning curves.
2. Learning curves for major liver resections due to metastatic tumours are similar to the learning curves of hemihepatectomies performed in primary liver malignancies, therefore, the type and character of a liver tumour (primary or metastatic) does not seem to influence the learning curve.
3. As expected, small liver resections were performed faster, with lower intraoperative blood loss levels, shorter postoperative stays, and fewer complications according to the Clavien−Dindo classification when compared to major liver resections.

4. Fewer procedures were needed to gain stabilization and repeatability in operating times and intraoperative blood loss levels in small liver resections compared to major liver resections.
5. Wedge liver resection performed as a part of cytoreductive surgery in women with advanced ovarian cancer can be performed safely and feasibly by gynaecologic oncologists.
6. Additionally, the wedge liver resections do not increase the risk of surgical complications, nor significantly affects operating time, intraoperative blood loss or postoperative hospital stay length.

5. Piśmiennictwo.

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A Retrospective, Single-Centre Study on the Learning Curve for Liver Tumor Open Resection in Patients with Hepatocellular Cancers and Intrahepatic Cholagangiocarcinomas

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Abstract: Background: Liver resections have become the first-line treatment for primary malignant tumors and, therefore, are considered a core aspect of surgical training. This study aims to evaluate the learning curve for the safety of open hemihepatectomy procedures for patients suffering from hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC). Methods: This single tertiary center retrospective analysis includes 81 consecutive cases of right or left hemihepatectmy. A cumulative sum (CUSUM) control chart was used to investigate the learning curve. Results: The CUSUM curve for operative time and blood loss level peaked at the 29th and 30th case, respectively. The CUSUM curve for minor adverse effects (mAEs) and severe adverse effects (sAEs) showed a downward slope after the 27th and 36th procedures; the curve, however, remained within the acceptable range throughout the entire study. Conclusion: When performing open hemihepatectomies in patients with HCC and ICC, the stabilization of the operative time and intraoperative blood loss level are gained earlier than sAEs risk reduction.

Keywords: hemihepatectomy; hepatocellular carcinoma (HCC); intrahepatic cholangiocarcinoma (ICC); learning curve

1. Introduction

Hepatocellurar carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two most common primary liver malignancies [1]. Factors which have been recognized as increasing the risk of those type of cancers include, i.e., chronic infection with the hepatitis B virus, exposure to aflatoxin B1, obesity, alcoholism, chronic infection with the hepatitis C virus, diabetes and the metabolic syndrome [2,3].

These two types of cancers usually occur in the more developed countries' populations [4,5]. In Poland, there were 26,280 cases identified in the country's male population between 1999 and 2016, with the standardized incidence rate oscillating between 3.78 and 5.51, and the mortality rate between 3.42 and 4.43. In the Polish population of women, the standardized incidence rate in the period analyzed fluctuated between 1.3 to 2.61, with the mortality rate at 4.23 up to 5.73 [6].

Primary liver malignancies show aggressive biology and unfavorable prognosis of recovery [7–9]. The basic treatment method of these types of cancer is a radical surgical resection [7,8,10]. Since these cancers are usually diagnosed in an advanced stage, extensive surgical procedures (including right-side or left-side hepatectomies) become necessary [9,10]. Nowadays, more and more non-invasive procedures (i.e., laparoscopic or robot-assisted) are being conducted.

There are already many studies published that analyze the learning curve for liver resection procedures implementing minimally invasive surgery [11–17]. Gulibaud et al. postulated that the learning curve for laparoscopic liver resections is a time-consuming process, and especially major laparoscopic liver resections must be implemented gradually under the supervision of experienced surgeons. Moreover, training outside the operating room may be helpful in gaining surgical experience and reduce adverse effects connected with these procedures [15]. Luft et al. concluded that liver major resections, when regionalized and limited to high-volume centers such as hospitals performing 200 or more of these operations annually, present significantly lower death rates compared with lower-volume centers [16]. For patients diagnosed with other malignancies than a primary liver malignant tumor (especially colorectal carcinoma), but also with confirmed liver metastases, the Italian Consensus recommends minimally invasive simultaneous resections for synchronous liver metastases [17].

The aim of this paper is a retrospective analysis of the learning curve for advanced liver resection techniques in open surgery, including right and left hemihepatectomy, taking account of patient safety parameters.

2. Materials and Methods

2.1. Patients and Procedures Characteristics

A retrospective analysis of the medical registry comprising patients who underwent laparotomy and liver tumor resection due to primary HCC or ICC was approved by the Institutional Review Board. The study covered the period 1 January 2010 until 31 December 2020, and all patients received surgery performed by the same surgeon—a specialist in general surgery and in training in hepatobiliary surgery. The inclusion criteria were as follows: (1) age 18 years or above, (2) primary HCC or ICC in histopathological reports, and (3) no previous liver surgeries; cases with missing data were excluded. As described in detail in our prior paper, the end points analyzed were following: (1) operating time measured from skin incision to skin closure; (2) intraoperative blood loss level, defined as blood volume removed by suction; (3) post-operative hospital stay length from the first post-operative day to the hospital discharge date [14]. All of the performed procedures were classified as left or right hemihepatectomies, according to the Brisbane 2000 Terminology of Liver Anatomy and Resections [18], and were considered as major liver resections. Similar to our former study, patient safety was evaluated based on the presence of adverse events (AE), an inevitable aspect of the medical services provided. These events were defined as minor AEs (mAEs), matching grade I-IIIa complications per the Clavien–Dindo classification, and severe Aes (sAEs), corresponding to grade IIIb-Ivb complications [19]. There were no grade V complications, e.g., patient's death, reported in this study. Grade I-IIIa complications included (1) wound infection, (2) prolonged hospital stay (>10 days), and (3) hematoma managed non-surgically. Grade IIIb-Ivb complications were as follows: (1) patient death, (2) admission to the intensive care unit, (3) reoperation due to intraperitoneal bleeding, (4) wound dehiscence requiring resuturing under general anesthesia, (5) hepatobiliary fistula requiring relaparotomy, and (6) post hepatectomy liver failure (PHLF) [14,19]. PHLF was defined according to the International Study Group of Liver Surgeries (ISGLS) consensus [20]. Preoperative Poratal Vain Embolisation (pPVE) was not performed in the analyzed cohort.

Due to extensive liver resection, in all of the cases that analyzed blood and/or frozen plasma, transfusions were not considered as adverse effects.

2.2. Basic Characteristics of Hepatobiliary Surgical Training

The Polish surgical training system does not provide a specialization in hepatobiliary surgery. That is why 30 years ago, our tertiary surgery unit established and then developed a proprietary tutoring program in that procedure. In the late 90's, one of our experienced general surgeons underwent two-year foreign training in hepatobiliary surgery and achieved skills and competences entitling to independently performed, complex surgical procedures on liver and the biliary tract. Upon his return, he began performing these procedures as well as supervising other doctors training in hepatobiliary surgery. Currently, the program is dedicated to specialists in general, colorectal and oncologic surgery, and is aimed at maintaining the potential of at least three well-skilled and experienced hepatobiliary surgeons in the unit. At present, one surgeon is training at a time and starts operating only after finishing the theoretical tutorial and assisting in at least 20 hepatobiliary procedures. The first 10 small liver resections (e.g., segmentectomy or bisegmentectomy according to the Brisbane 2000 terminology [19]) and the first 15 major liver resections (e.g., right/left hemihepatectomy resection or right/left extended hepatectomy according to the Brisbane 2000 terminology [19]) the trainee performs are under the direct supervision of an experienced hepatobiliary surgeon. Subsequently, they operate without direct control, however, an experienced hepatobiliary consultant who is not a member of surgical team is available in the operating theatre throughout the whole surgery. Such a procedure is safe for the patient, and it also allows the surgeon in training to develop their own competences and gain experience. Before every procedure, each patient is advised about the type of surgery they are about to undergo, the possible risks and complications, as well as the names of surgical team members. In this way, patients' informed consent is secured. If the patient does not agree to be operated on exclusively by the operating team, the surgery is led by a consultant in hepatobiliary surgery, not the trainee. During the procedure, the operating time and intraoperative blood loss is recorded; incidence of complications and the post-operative stay length is also collected together with the standard medical data.

2.3. Statistical Analysis

Similar to our former study which investigated the learning curve for hemihepatectomy in patients with primary liver neoplasms, a cumulative sum control chart (CUSUM) analysis was used to examine the learning curve in terms of operative time as well as intraoperative blood loss level and hospital stay length [12–14]. Body mass index (BMI) was calculated by dividing the body mass by the square of the body height and is presented as kg/m^2. Data are presented as the mean $\pm$ standard deviation (SD) or as the median $\pm$ standard error of the mean (SEM) depending on their distributions, which were checked using the Kologomorov–Smirnov test. To compare the groups of patients with HCC and ICC, the parametric Student's t-test, the nonparametric Mann–Whitney U test and the chi-squared test were used as appropriate. For evaluating categorical data, the chi-squared test was employed. A p value of 0.05 was considered statistically significant, and all the calculations were performed using STATISTICA data analysis software, version 12.0 (StatSoft, Inc. (www.statsoft.pl) 2019. STATISTICA data analysis software system, version 12.), and MedCalc Statistical Software (MedCalc Software Ltd.; Ostend, Belgium).

3. Results

3.1. Patients and Procedure

From the total number of 87 identified cases, 5 were excluded due to missing data, and as a result, 82 cases were analyzed. Patients suffering from ICC were significantly younger and presented lower BMI compared to patients diagnosed with HCC. A total of 68 (82.93%) patients had cholecystectomy performed at the time of liver resection, while 14 (17.07%) were after a former cholecystectomy (11 laparoscopically and 3 with laparotomy). This, however, did not significantly influence the median operating time (275.00 min; IQR: 107.00 vs. 262.00 min; IQR: 165.00; $p = 0.245$), intraoperative blood loss (340.00 mL; IQR: 102.00 vs. 372.00 mL; IQR: 55.00; $p = 0.325$), total hospital stay (9.0 days; IQR: 10.0 vs. 13.00

days; IQR: 7.00; p = 0.254) or ICU stay (0.0 days; IQR: 1.0 vs. 0.00 days; IQR: 2.00; p = 0.128). Open right hemihepatectomy was performed in 59 (71.95%) cases, while open left hemihepatectomy in 23 (28.05%) cases. Detailed characteristics of the patients are presented in Table 1.

Table 1. Baseline patients characteristics to the type of cancer, respectively.

	Total (N = 82)	**HCC % (N = 61)**	**ICC %% (N = 21)**	**p ***
Mean age (±SD $) [years]	55.07 (±11.54)	60.95 ± 7.32	53.05 ± 12.21	0.006 **
Mean BMI $$ (±SD $) [kg/m^2]	23.94 (±3.39).	24.52 ± 3.44	22.26 ± 42.64	0.008 **
Male (%)/Female (%)	47 (57.32%)/ 35 (42.68%)	35 (57.38%)/ 26 (45.62%)	13 (59.10%)/ 8(40.90%)	0.716
Median operating time (IQR $$$) [min]	255 (IQR: 110)	250 (IQR: 105)	290 (IQR: 60)	0.245
Median intraoperative blood loss (IQR $$$) [mL]	342 (IQR: 185)	355 (IQR: 310)	340 (IQR: 315)	0.232
Median post-operative hospital stay (IQR $$$) [days]	10 (IQR: 9)	11 (IQR: 9)	6 (IQR: 7)	0.060
Number of grade I-IIIa complications according to the Clavien–Dindo classification (%) 1. wound infection 2. prolonged hospital stay (>10 days) 3. hematoma managed nonsurgically	6 (9.84%) 25 (30.86%) 9 (14.75%)	4 (9.84%) 18 (42.62%) 7 (14.75%)	2 (9.84%) 8 (42.62%) 2 (14.75%)	0.467
Number of grade IIIb-V complications according to the Clavien–Dindo classification (%) 1. Patient death 2. Admission to the intensive care unit 3. Reoperation due to intraperitoneal bleeding 4. Wound dehiscence 5. Hepatobiliary fistula 6. Post-hepatectomy liver failure (PHLF)	0 (0.00%) 14 (17.07%) & 4 (4.88%) 5 (6.10%) 2 (2.44%) 3 (3.66%) &	0 (0.00%) 10 (16.39%) 3 (4.92%) 3 (4.92%) 2 (3.29%) 2 (3.29%)	0 (0.00%) 4 (19.05%) 1 (4.76%) 2 (9.52%) 0 (0.00%) 1 (4.76%)	0.677
Incidence of Pinard's maneuver (%)	39 (47.56%)	29 (47.54%)	10 (47.62%)	0.997
Median time of Pringle's maneuver (IQR $$$) [min]	15 (IQR: 30)	15 (IQR: 30)	15 (IQR: 15)	0.687
Prevalence of preoperative anemia (defined as hemoglobin level < 12.0 and or hematocrit level < 35.0)	28 (34.15%)	20 (32.79%)	8 (38.10%)	0.878
Prevalence of right/left hemihepatectomy && (%)	52 (63.41%)/ 30 (36.59%)	41 (67,21%)/ 20 (32,79%)	11 (52.38%) 10 (47.62%)	0.224
Prevalence of liver cirrhosis cirrhosis (%)	59 (62.19%)	50 (81,97%)	9 (42.86%)	0.001 **
Median preoperative ASA &&& score IQR $$$)	3 (IQR: 1)	3 (IQR:1)	2 (IQR: 1)	0.754

$ SD—standard deviation; $$ BMI—body mass index; $$$ IQR—interquartile range; % HCC—hepatocellular carcinoma; %% ICC—Intrahepatic cholangiocarcinoma; & 2 cases of post-hepatectomy liver failure required admission intensive care unit, therefore, the total number of patients with grade IIIb-IVb according to the Clavien–Dindo classification is 26, while the total number of complications grade I-IIIc according to the Clavien–Dindo classification is 28; && according to the Brisbane 2000 terminology [19]; &&& ASA—the American Society of Anesthesiologists Physical Status Classification System; * compared between HCC and IHC; ** statistically significant p-value.

3.2. Learning Curve Endpoints

In the whole cohort, the median operating time was 255 min (IQR: 110), the median intraoperative blood was 342 mL (IQR: 154), and the median post-operative hospital stay was 10 days (IQR: 9). There were no significant differences between patients with HCC and ICC concerning the presented variables (see Table 1).

Based on operating time, the CUSUM analysis identified procedure no. 29 as the cut-off point of gaining stable and repeatable surgical experience (Figure 1). Procedures 1–29 were classified as "time early" (tE), while cases 30–82 as "time late" (tL). Median operating time (350.00 min (IQR: 65.00) vs. 220 min (IQR: 80.00); $p < 0.001$) and blood loss level (750.00 mL (IQR: 885.00) vs. 310 mL (IQR: 100.00); $p < 0.001$) were significantly higher in the tE group compared to the tL procedures. Additionally, in the tE cohort, the median postoperative hospital stay was significantly longer compared to the tL hospitalizations (15.00 days (IQR: 10) vs. 7 days (IQR: 6); $p < 0.001$). No significant differences in patients' mean age and mean BMI were observed between the analyzed groups.

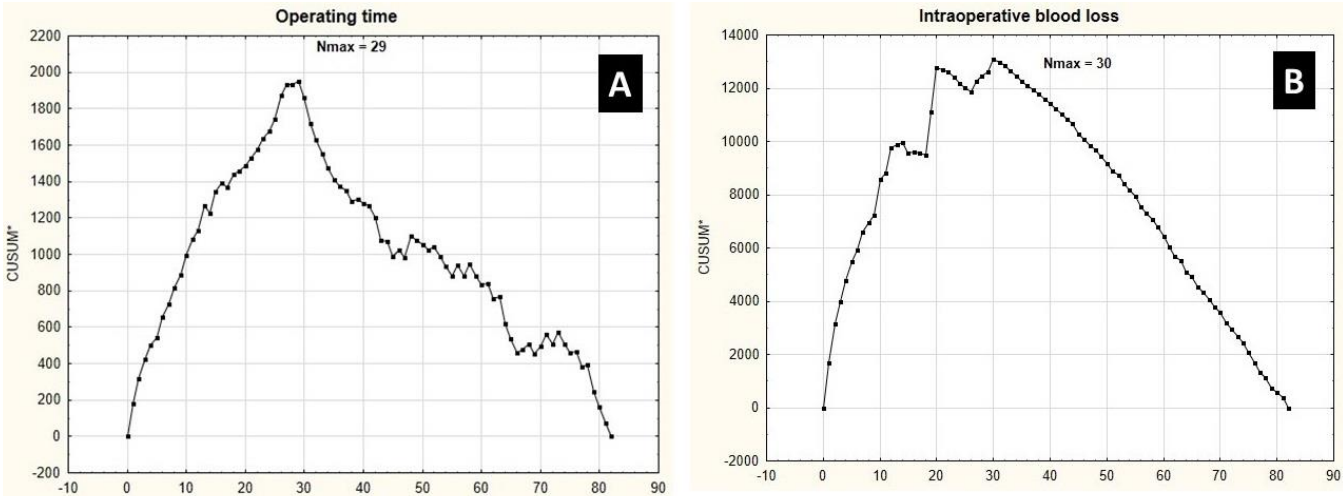

Figure 1. Cumulative sum control chart of operative (CUSUM*) operating time (**A**) and intraoperative blood loss (**B**) against the number of patients.

When focusing on the intraoperative blood loss level, the cut-off point for the learning curve was procedure no. 30—this allowed us to distinguish procedures 1–30 as tE and 31–82 as tL. Similarly to previous results, we observed significantly longer operative times (335.00 min (IQR: 65) vs. 222.00 min (IQR: 82); $p < 0.001$), higher level of intraoperative blood loss (775 mL (IQR: 885) vs. 300.00 mL (IQR: 130); $p = 0.001$) and prolonged post-operative hospitalization (15 days (IQR: 10) vs. 7 days (IQR: 5.5); $p < 0.001$) in the tE cohort compared to the tL group. Again, no significant differences in patients' mean age and mean BMI were observed between the above groups.

3.3. Patient Safety

In the entire cohort, 40 (48.78%) minor and 28 (34.15%) severe adverse effects occurred (see Table 1). Two cases of post-hepatectomy liver failure required admission to the intensive care unit, therefore, the total number of patients with sAEs is 26, while the total number of sAEs is 28. Additionally, 23 (28.39%) patients required blood and/or frozen plasma transfusions—these were not analyzed as adverse effects.

Furthermore, the CUSUM analysis showed that the incidence of mAEs decreased after the 26th procedure, which was consistent with the operative time and comparable in intraoperative blood loss level (Figure 2). For sAEs, a stable decrease in sAEs was accomplished after the 37th procedure, which was significantly higher than the operative time and intraoperative blood loss peak points. As expected, mAEs and sAEs occurred more frequently during procedures 1–26 (17/26 (73.91%) vs. 23/59 (38.98%); $p = 0.001$ and 16/26 (61.53%) vs. 10/59 (16.95%); $p < 0.001$, respectively) and 1–39 (25/39 (58.97%) vs. 17/43 (39.53%); $p = 0.002$ and 21/37 (56.76%) vs. 5/45 (11.11%); $p < 0.001$, respectively).

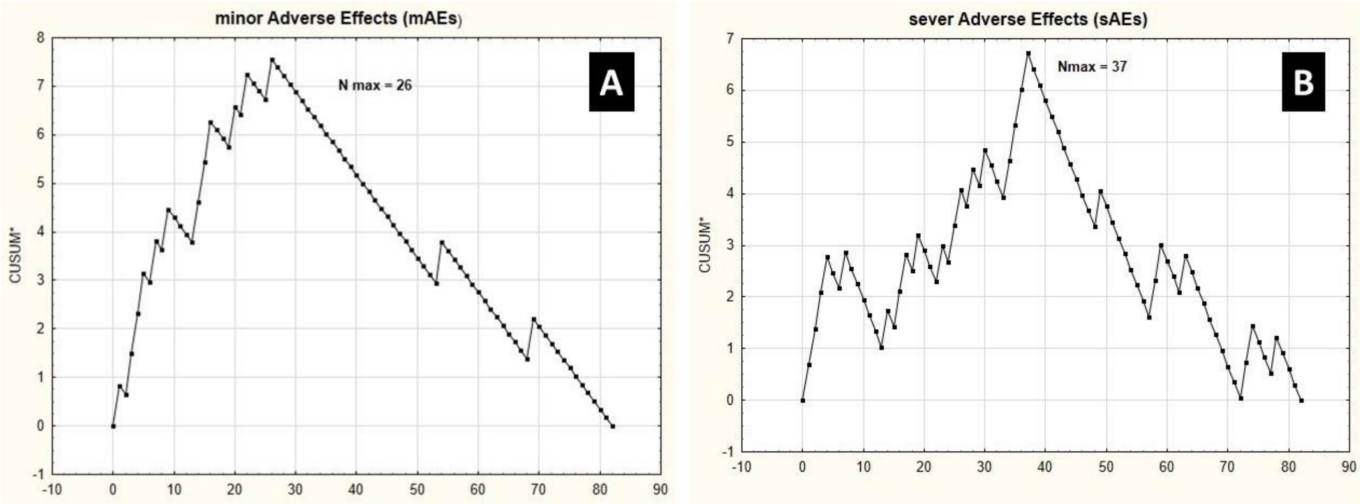

Figure 2. Cumulative sum control chart of operative (CUSUM*) minor adverse effects (mAEs) corresponding with grade I-IIIa complications according to the Clavien–Dindo classification (**A**) and severe adverse effects (mAEs) (**B**) matched with grade IIIb-V complications according to the Clavien–Dindo classification against the number of patients.

4. Discussion

A literature review brought us to a conclusion that, although these procedures are essential for residency training in general and oncologic surgery specializations, there has been only a few studies evaluating the learning curve for open liver surgery, and what is more, the studies carried out so far usually compare these with the laparoscopic or robotic approach [14,21–25]. Since hemihepatectomies—robotic, laparoscopic, and open—are univocally considered as major liver surgeries, only these procedures were analyzed in our study [21,22]. Based on operating time and intraoperative blood loss analysis, we demonstrated comparable learning curves for open hemihepatectomy in patients with HCC and ICC. The results we obtained are similar to our previous findings on learning curves in the management of metastatic liver tumors of colorectal cancer with open liver surgery [14]. In that paper, we showed that operating time and intraoperative blood loss stabilized after 26th and 24th major liver resection procedures [14]. These findings indicate that the type of liver malignancy is not the most essential factor determining the learning curve in open liver surgery.

However, in an investigation of 299 patients with HCC who underwent open liver resection, Navarro et al. showed that the learning curve was maximized after 42 cases [24]. This stands in contrast to our findings, in which operating time stabilization was reached after the 29th and intraoperative blood loss after the 30th procedure. In this study, however, both the laparoscopic and open approaches were analyzed and compared with open liver resections; laparoscopic liver resections had higher liver-related injury and complications levels during the learning phase, which can result in a certain bias. Nevertheless, in our cohort, the mAEs risk reduction was obtained after 36 procedures and that number is similar to the results reported by Navarro et al. [24].

Many authors who investigated the safety of (mainly laparoscopic) liver resection procedures consider the need for blood and/or fresh plasma transfusion as a sAE, which is consistent with the approach used in our previous study, concerning the small and major liver resection safety in patients with metastatic liver tumors [14,25–27]. In this study, focusing on major liver resections in patients with primary cancers, we did not consider any type of transfusion as a sAE.

The main strength of this study is the large number of consecutive cases of hemihepatectomy procedures performed in patients with primary liver malignancies. Additionally, separate operating time, intraoperative blood loss, and AEs analyses provide a new insight into the process of acquiring surgical skills and experience. We are, however, aware that the present series had several limitations. Firstly, this report was based on the experience of one surgeon with some already established surgical techniques. Some authors state that when studying the learning curves for open surgical techniques, one should evaluate a whole team rather than a single surgeon. Nishikimi et al., for instance, postulated that surgery for advanced ovarian cancer cannot be performed by a single surgeon as it involves a wide operative field in the peritoneal cavity and requires assistant surgeons [28]. There are similar conditions in open liver surgery procedures, especially when major resection is performed. Secondly, a retrospective analysis may be biased due to unknown or unidentified factors that, under some circumstances, can influence the final results.

5. Conclusions

- Hemihepatectomy procedures present similar learning curves to achieve stabilization in operating time and intraoperative blood loss.
- Operative time and intraoperative blood loss cannot be, however, considered as surrogates for the risk of grade IIIb-IVb complications, according to the Clavien–Dindo classification, as they present significantly different learning curves [19].
- Learning curves for major liver resections due to metastatic tumors are similar to our findings; therefore, the type and character of a liver tumor (primary or metastatic) does not seem to influence the learning curve.

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Informed Consent Statement: The patient consent obtained for the surgical procedures was not mandatory for data analysis as the study involved retrospective analysis of anonymous data.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to restrictions.

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

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Learning Curve for Metastatic Liver Tumor Open Resection in Patients with Primary Colorectal Cancer: Use of the Cumulative Sum Method

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Abstract: Background: Liver resections have become the first-line treatment for primary and metastatic tumors and, therefore, are considered a core aspect of surgical training. This study aims to evaluate the learning curve of the extent and safety of liver resection procedures for patients with metastatic colorectal cancer. Methods: This single tertiary center retrospective analysis includes 158 consecutive cases of small liver resection (SLR) (n = 107) and major liver resection (MLR) (n = 58) procedures. A cumulative sum control chart (CUSUM) method was used to investigate the learning curve. Results: The operative time, total blood loss level, and incidence of adverse effects showed a learning curve. For SLRs, the CUSUM curve for operative time and blood loss level peaked at the 19th and 17th case, respectively, while for MLRs, these curves peaked at the 28th and 24th case, respectively. The CUSUM curve for minor adverse effects (MAEs) and severe adverse effects (SAEs) showed a downward slope after the 16th and 68th procedures in the SLRs group and after the 29th and 39th procedures in the MLRs cohort; however, it remained within the acceptable range throughout the entire study. Conclusion: SLR procedures were performed faster with less intraoperative blood loss and shorter postoperative stays than MLRs, and a higher number of completed procedures was required to gain stabilization and repeatability in the operating time and intraoperative blood loss level. In MLR procedures, the reduction of SAEs was accomplished significantly later than the stabilization of the operative time and intraoperative blood loss level.

Keywords: learning curve; major liver resections; metastatic liver tumor; small liver resections

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1. Introduction

The liver is a critical organ and a common metastatic site of many malignancies, including breast, colorectal, lung, ovarian, and gastric cancers, gastrointestinal stromal tumors (GISTs), and melanomas [1–8]. These metastases can be recognized synchronously with primary tumor diagnoses or can occur up to decades after the primary radical treatment completion. Colorectal cancer has a high liver metastatic potential. The proportion of patients with synchronous liver metastases diagnosed with primary tumors varies from 14.5% to 26.5%, and patients are more often diagnosed with left-sided than right-sided colon cancer [1,2,9]. In a five-year follow-up study, the incidence of liver metastases in colorectal cancer survivors increased up to 30% [2,9]. Surgical treatment is a first-choice therapy for liver metastases; therefore, every surgeon, including both general surgery and oncologic surgery specialists, should be able to effectively manage patients with primary and secondary liver tumors.

A surgeon's necessary skills and experience acquisition can be evaluated utilizing established learning curves. Using this method, the minimum number of procedures required to reach the same intra- and postoperative outcomes by a surgeon applying a given technique can be predicted. The skills acquisition progression can be presented graphically, helping to identify the point of improvement [10].

To identify inflection points corresponding to the learning curve, a cumulative sum analysis (CUSUM) may be used [11]. Originally, this technique was primarily employed for monitoring performance and detecting areas for improvement in the industrial sector; thereafter, in the late 1970s, it was adopted for analyzing learning curves first for surgical procedures and then for various other medical methods [12,13].

Since then, many studies have evaluated learning curves in liver surgery. These studies mostly focused on primary tumors and compared different surgical approaches, including minimally invasive techniques such as laparoscopic liver resection, robotic surgery, and hepatectomies for liver transplantations [14–17]. However, the balance between the learning curve and length of postoperative hospital stay as well as minor adverse effects (MAEs) and severe adverse effects (SAEs) has never been specifically investigated. The primary aim of this study was to define a standard educational path for evaluating the learning curve based on the operation time and intraoperative blood loss level in patients with colorectal cancer. The secondary endpoint analyzed was patients' length of postoperative hospital stay and occurrence of MAEs and SAEs in the context of a learning curve.

2. Materials and Methods

2.1. Patient and Procedures Characteristics

A retrospective analysis of the medical registry comprising patients who underwent laparotomy and liver tumor resection due to metastases was approved by the Institutional Review Board. The study covered the period from 01 January 2010 until 31 December 2015, and all the patients received surgery performed by the same surgeon—a specialist in general surgery and in training in hepatobiliary surgery. The inclusion criteria were as follows: (1) aged 18 years or above, (2) liver metastases of colorectal cancer confirmed in histopathological reports, and (3) no previous liver surgeries; cases with missing data were excluded. The endpoints analyzed were as follows: (1) operating time measured from skin incision to skin closure; (2) intraoperative blood loss level, defined as blood volume removed by suction; and (3) postoperative hospital stay length from the first postoperative day to hospital discharge date. Procedures including left or right were considered major liver resections (MLRs). Additionally, two cases of formal posterior segments 6 and 7 resections were included in the MLRs group, because they presented outliers in operating time and intraoperative blood loss if considered small liver resections (SLRs). Nonanatomical tumor excisions and segments 1, 2, 3, 4b, 5, and 8 resections were described as SLRs. Patient safety was evaluated based on the presence of adverse events, an inevitable aspect of the medical services provided, and these events were defined as MAEs and SAEs. MAEs included: (1) wound infection; (2) prolonged hospital stay (>10 days); and (3) hematoma managed nonsurgically. SAEs were as follows: (1) patient death; (2) admission to the intensive care unit; (3) reoperation due to intraperitoneal bleeding; (4) wound dehiscence; (5) hepatobiliary fistula; and (6) blood and/or frozen plasma transfusions. Only two cases of posthepatectomy liver failure (PHLF)—as defined per the International Study Group of Liver Surgeries (ISGLS) consensus—were reported in the MLRs group, therefore, they were withdrawn for further analysis [18].

2.2. Statistical Analysis

A cumulative sum control chart (CUSUM) analysis was used to investigate the learning curve of SLRs and MLRs separately in terms of operative time as well as intraoperative blood loss level and the length of hospital stay [12,13,19]. The cumulative difference between the values of each patient's variables and the mean variable values was plotted with the patients arranged chronologically. The change point identified in the CUSUM curve was the point that divided SLRs and MLRs into early and late groups based on the operative time (time early: tE; time late: tL), the intraoperative blood loss level (blood loss early: blE, and blood loss late: blL), and the length of postoperative hospital stay (postoperative hospital stay early: hE, and postoperative hospital stay late: hL). Body mass index (BMI) was calculated by dividing the body mass by the square of the body height and is presented as kg/m2. Data are presented as the mean ± standard deviation (SD) or as the median ± standard error of the mean (SEM) depending on their distributions, which were checked using the Kologomorov–Smirnov test. Then, the study groups were compared using the parametric Student's t-test and the nonparametric Mann–Whitney U test as appropriate. For evaluating categorical data, the chi-squared test was employed. A p value of 0.05 was considered statistically significant, and all the calculations were performed using STATISTICA data analysis software, (TIBCO Software Inc. 2017, version 13.0, Palo Alto, CA, USA).

3. Results

3.1. Patients and Procedure

From the total number of 169 identified cases, 4 were excluded due to missing data, and in 7, metastases were not confirmed in the final pathological report. Accordingly, 158 cases were analyzed. The median time from primary colorectal surgery was 45 months (IQR: 36). A total of 107 cases (67.73%) were classified as SLRs and 51 (32.27%) as MLRs based on the criteria described in the Methodology section. The study group comprised 76 (49.10%) males and 82 (51.90%) females of a mean age of 57.60 years (±13.03) and a mean BMI of 26.88 kg/m^2 (±4.57). Detailed characteristics of the patients and procedures are presented in Table 1.

Table 1. Baseline characteristics of patients and procedures.

	Total (n = 158)	SLRs [%] (n = 107)	MLRs [%%] (n = 51)	*p* *
Mean age (±SD [$]) [years]	57.60 (±13.03)	58.20 (±13.89)	56.31 (±11.03)	0.407
Mean BMI [$$] (±SD [$]) [kg/m^2]	26.88 (±4.57)	26.80 (±4.61)	27.08 (±4.52)	0.731
Male (%)/Female (%)	82 (51.90%)/ 76 (48.10%)	55 (51.40%)/ 52 (49.60%)	27 (52.94%)/ 24 (47.06%)	0.856
Median operating time (IQR [$$$]) [min.]	205 (IQR: 165)	170 (IQR: 600)	400 (IQR: 195)	<0.001 **
Median postoperative hospital stay (IQR [$$$]) [days]	6 (IQR: 3)	5 (IQR: 3)	8 (IQR: 7)	0.016
Median intraoperative blood loss (IQR [$$$]) [mL]	330 (IQR: 540)	170 (IQR: 155)	450 (IQR: 980)	<0.001 **
Number of minor adverse effects (%)	71 (44.94%)	46 (42.99%)	25 (49.02%)	0.476
Number of severe adverse effects (%)	28 (17.72%)	15 (14.02%)	13 (25.49%)	0.077
Incidence of Pringle's manouver (%)	81 (51.27%)	58 (54.21%)	23 (45.10%)	0.284
Median time of Pinard's manouver (IQR [$$$]) [min.]	15 (IQR: 30)	15 (IQR: 30)	30 (IQR: 15)	0.534

[$] SD-standard deviation; [$$] BMI-body mass index; [$$$] IQR-interquartile range; [%] SLRs-small liver resection procedures; [%%] MLRs-major liver resection procedures; * compared between MLRs and MLRs; ** statistically significant *p* value.

3.2. Learning Curve Endpoints

The median operating time in the 158 consecutive cases was 205 min (IQR: 33) and was significantly shorter in SLR procedures than in MLRs (see Table 1). The median intraoperative blood loss level in the whole cohort was 330 mL (IQR: 45), and similar to the operating time, it was significantly lower in the SLRs group than in the MLRs group (see Table 1). In SLR procedures, based on operating time, CUSUM analysis identified procedure no. 19 as the cut-off point of gaining a stable and repeatable surgical experience; in MLRs, this point was established at procedure no. 28 (Figure 1).

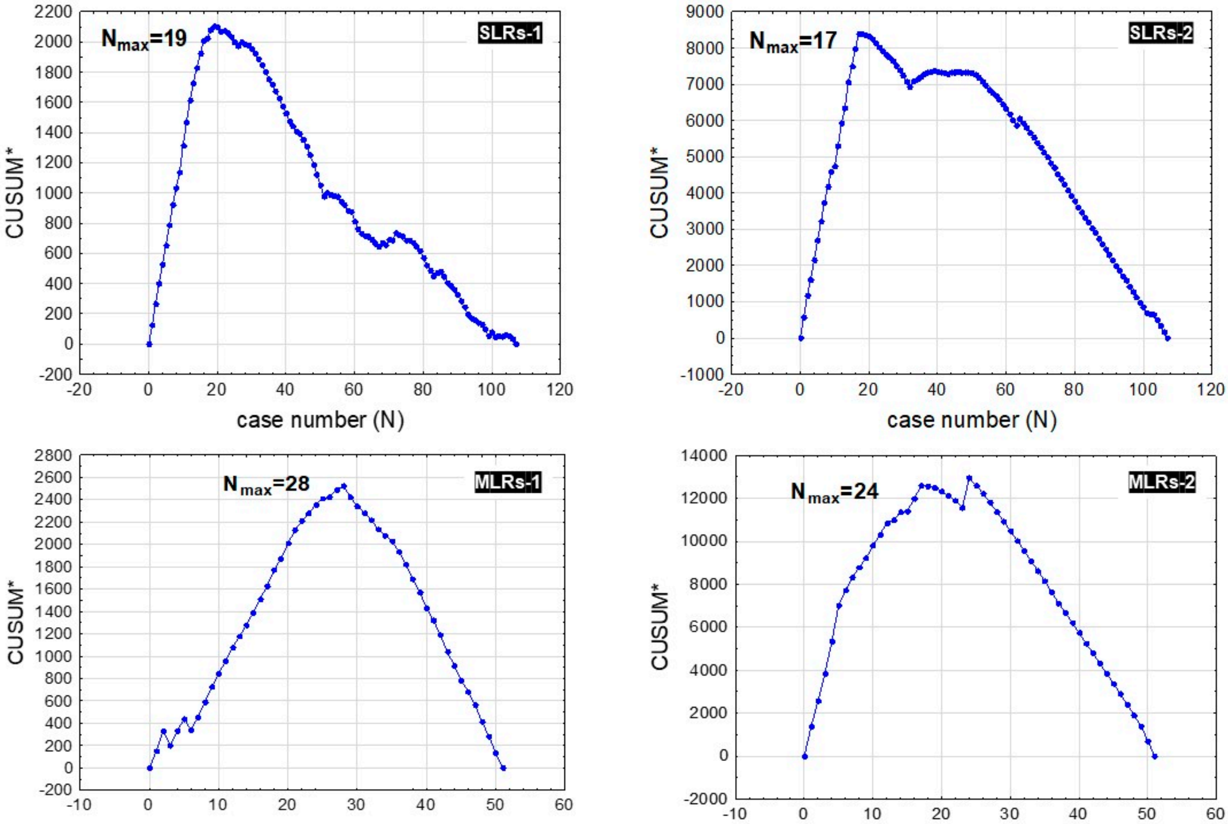

Figure 1. Cumulative sum control chart of operative (CUSUM *) time (SLRs-1) and intraoperative blood loss (SMLRs-2) against the number of patients with small liver resections (SMLs), and CUSUM time (MLRs-1) and intraoperative blood loss (MLRs-2) against number of patients with major liver resections (MLRs); N = 107.

Subsequent analysis showed that in the tE-SLRs group (defined as procedures no. 1–19), the median operating time was longer [310 min. (IQR: 40) vs. 135 min. (IQR: 35); $p < 0.001$]; similarly, the median intraoperative blood loss level was higher [750 mL. (IQR: 150) vs. 150 mL. (IQR: 118); $p < 0.001$], and the median postoperative hospital stay length was longer [7 days (IQR: 4) vs. 5 days (IQR: 2); $p = 0.001$] compared to those observed in tL-SLRs procedures (i.e., 20–107), and the differences were significant. No differences in patients' median age and BMI were observed between the analyzed tE-SLRs and tL-SLRs groups [54.58 years ± 14.90 vs. 58.98 years ±13.62; $p = 0.565$ and 27.27 kg/m^2 ± 4.49 vs. 26.69 kg/m^2 ± 4.65; $p = 0.909$].

In the MLR group, based on the learning curve and CUSUM results, procedures no. 1–28 were classified as tE-MLRs, while cases no. 29–51 were classified as tL-MLRs. No differences in mean patient age or mean BMI were observed between the tE-MLR and tL-MLR procedures [57.84 years ±13.41 vs. 55.47 years ± 9.47; $p = 0.463$ and 25.74 kg/m^2 ± 3.33 vs. 27.50 kg/m^2 ± 4.80; $p = 0.286$]. In the tE-MLR group, compared with the tL-MLR cohort, we observed a significantly longer operative time [460 min. (IQR: 25) vs. 285 min. (IQR: 67.5); $p < 0.001$] and an increased intraoperative blood loss level [1400 mL (IQR: 800) vs. 352 mL (IQR: 37.5); $p < 0.001$] with a prolonged postoperative hospital stay length [12 days (IQR: 37) vs. 6.5 days (IQR: 3); $p = 0.003$], and these differences were significant.

When taking into consideration intraoperative blood loss level cut-off points for the learning curve, procedure no. 17 for SLRs and no. 24 for MLRs allowed us to distinguish tE-MLRs (no. 1–17) and tL-MLRs (no. 18–107) (Figure 1). No significant differences in mean patient age or mean BMI were observed between blE-SLRs and blL-SLRs [53.35 years ± 15.31 vs. 59.11 years ± 13.51; $p = 0.447$ and 26.81 kg/m^2 ± 4.47 vs. 26.79 kg/m^2 ± 4.66;

$p = 0.992$]. In the blE-SLRs group, however, we observed significantly longer operative times [310 min. (IQR: 30) vs. 165 min. (IQR: 35); $p < 0.001$], increased intraoperative blood loss levels [800 mL (IQR:140) vs. 152.5 mL (IQR: 115); $p < 0.001$], and prolonged postoperative hospital stays [7 days (IQR: 4) vs. 5 days (IQR: 2); $p = 0.002$] compared with those observed in the blL-SLRs cohort.

Again, based on the learning curve and CUSUM results in the MLRs group, procedures no. 1–24 were classified as blE-MLRs, while cases no. 25–51 were classified as blL-MLRs, and no significant differences in mean patient age or mean BMI were observed between blE-MLRs and blL-MLRs [55.68 years ± 13.34 vs. 57.01 years ± 8.64; $p = 0.674$ and 27.23 kg/m^2 ± 4.72 vs. 26.99 kg/m^2 ± 4.99; $p = 0.870$]. A significantly longer operative time [455 min. (IQR: 30) vs. 267 min. (IQR: 125); $p < 0.001$], an increased intraoperative blood loss level [1320 mL (IQR: 700) vs. 340 mL (IQR: 45); $p < 0.001$], and a prolonged postoperative hospital stay [10 days (IQR: 18) vs. 7 days (IQR: 3); $p = 0.031$] were observed in the blE-MLRs cohort compared with those in the blL-MLRs group.

3.3. Patient Safety

In the entire SLR cohort, 22 (20.56%) minor and 15 (14.08%) severe adverse effects occurred, including: for MAE, (1) wound infection—5; (2) prolonged hospital stay (>10 days)—11; (3) nonsurgically managed hematoma—8; and for SAE, (1) reoperation due to intraperitoneal bleeding—4; (2) wound dehiscence3; and (3) blood and/or frozen plasma transfusions—11. In the tE-SLR group, both MAEs and SAEs were observed more frequently than in the tL-SLRs cohort [10/19 (52.63%) vs. 12/88 (13.63%); $p < 0.001$ and 6/19 (31.57%) vs. 9/88 (10.23%); $p = 0.002$, respectively]. Similarly, both MAEs and SAEs were observed more frequently in blE-SLRs than in blL-SLRs procedures [9/17 (52.94%) vs. 13/90 (14.44%); $p < 0.008$ and 6/17 (35.29%) vs. 9/90 (10.00%); $p = 0.025$].

In the MLR cohort, 25 (49.02%) MAEs and 13 (25.49%) SAEs occurred. MAEs included: (1) wound infection—6; (2) prolonged hospital stay (>10 days)—14; and (3) nonsurgically managed hematoma—6. SAEs were as follows: (1) patient death—1; (2) admission to intensive care unit—2; (3) reoperation due to intraperitoneal bleeding—2; (4) hepatobiliary fistula—2; and (6) blood and/or frozen plasma transfusions—5.

In the tE-MLR group, both MAEs and SAEs were observed more frequently than in the tL-MLR cohort [21/28 (75.00%) vs. 4/23 (17.39%); $p = 0.013$ and 10/28 (32.14%) vs. 3/23 (26.08%); $p = 0.149$, respectively]; however, the latter was statistically insignificant. Both MAEs and SAEs were observed more frequently in blE-MLRs than in blL-MLRs: 18/28 (64.29%) vs. 7/23 (30.43%); $p = 0.152$ and 8/28 (28.57%) vs. 5/23 (21.74 %); $p = 0.667$], but the differences were insignificant. Furthermore, the CUSUM analysis of MAEs and SAEs showed that in the SLRs cohort, the incidence of MAEs decreased after the 19th procedure, which was consistent with the operative time and intraoperative blood loss level; however, a stable decrease in SAEs was accomplished after the 61st procedure, which was significantly higher than the operative time and intraoperative blood loss peak points. In the MLR group, the MAE stabilized after the 29th procedure, and stabilization of SAEs was observed after the 39th procedure, significantly later than operative time and intraoperative blood loss level equilibrium point (Figure 2).

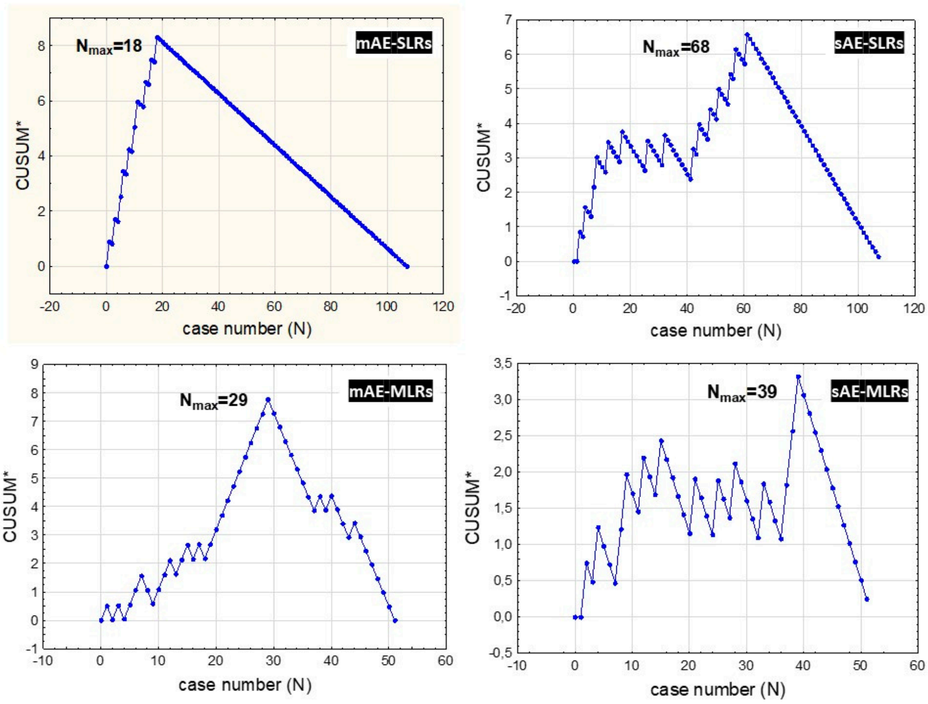

Figure 2. Cumulative sum control chart of operative (CUSUM *) minor adverse effects (MAEs) and severe adverse effects (SAEs) against the number of patients with small liver resections (SMLs) and CUSUM MAEs and SAEs against the number of patients with major liver resections (MLRs); N = 107.

4. Discussion

In this study, we demonstrated different learning curves for SLRs and MLRs procedures based on operating time and intraoperative blood loss analysis. Although simultaneous resections of segments 6 and 7 are not routinely classified as MLRs, according to our experience, these procedures require extended operating time and result in higher blood loss compared to others bisegmentomies. A similar classification was also presented in the 2008 Louisville Statement that defined MLRs as hemihepatectomies, trisectionectomies, and resection of the difficult posterior segments (that is, segments 4a, 6, and 7) which should be practiced in high-volume centers [20]. Additionally, our classification of liver resection is consistent with Chan et al.'s study which analyzed the learning curve for major hepatectomy in 151 patients who underwent 156 laparoscopic liver resections, thus making our results comparable with other studies [14].

As expected, fewer procedures are required to gain operating time and intraoperative blood loss level stabilization for SLRs than for MLRs. Additionally, SLR procedures exhibited shorter operating times and lower intraoperative blood loss levels than MLRs. These results are similar to Chan et al.'s findings, who reported shorter operating times, lower blood loss levels, and shorter hospital stay lengths for minor hepatectomies than for major hepatectomies [14]. However, it must be emphasized that our results cannot be directly compared with Chan et al.'s, who used a laparoscopic approach, as we performed open liver resections. Additionally, in that study, the learning curve analysis was applied only to major hepatectomies, identifying procedure no. 25 as a cut-off point distinguishing early from late procedures, which is comparable with our conclusions. In contrast to the above results, Nomi et al. analyzed 173 patients undergoing major hepatectomy procedures and, based on operating time, identified a three-phase learning curve with an initial stage comprising 45 cases [15]. In this study, however, the laparoscopic approach was analyzed, and a heterogeneous group of patients comprised cases of malignant and benign tumors as well as primary and metastatic liver cancers; thus, these results cannot be directly related to our conclusions [15]. Comparing laparoscopy versus laparotomy in small liver resections, Morino et al. confirmed a longer operating time but lower blood loss level in the laparoscopic group [21]. However, the mortality and morbidity rates in the two groups were comparable [21]. Similarly, Memeo et al., who analyzed 45 patients treated with laparoscopic liver resection and matched them with open liver resection cases, concluded that the laparoscopic approach resulted in shorter operative times, better resection margins, lower postoperative complications, and shorter hospital stays [22]. Similarly, de Sandro et al. indicated that, for patients with hepatocellular carcinoma, minor laparoscopic liver resection is a safe and feasible procedure, especially for cases complicated with liver cirrhosis, with fewer postoperative complications, lower operative blood loss levels, and shorter hospital stays along with comparable survival and recurrence-free survival rates [23]. The largest cohort of 782 hepatectomies was analyzed by Vigano et al., who found that liver resection with a laparoscopic approach is a safe operating technique and feasible for both primary and metastatic liver malignancies [24].

However, the novelty of the present study is a detailed analysis of patient safety based on MAE and SAE incidences using CUSUM testing. It has demonstrated that the most often analyzed indicators such as operating times and intraoperative blood loss levels are not simple surrogates for patient safety, especially in major liver resection surgeries. Our study shows that operation times and intraoperative blood loss levels stabilize significantly earlier, along with complications risk reduction and patient safety improvement. According to our analysis of MLR procedures, operative time improvement is gained after 28 procedures, while intraoperative blood loss is reduced even earlier—after completing 24 operations. Nevertheless, a significant reduction in SAEs in the MLR group was achieved only after as many as 39 operations. In the SLRs group, this was observed after even more—69 procedures. This can be explained by the two-fold larger SLRs group and the lower incidence of SAEs in this cohort than in the MLR cohort.

The main strength of this study is the large number of consecutive cases, especially SLRs. Additionally, separate analyses performed for SLR and MLR procedures provide new insight into the process of acquiring surgical skills and experience. We are, however, aware that the present series has several limitations. Firstly, this report was based on a single surgeon's experience with established surgical techniques and did not include different operators. Secondly, we recognize that a retrospective analysis may be biased due to unknown or unidentified factors that, under some circumstances, can influence the final results.

5. Conclusions

- As expected, SLR procedures were performed faster and with less intraoperative blood loss levels, shorter postoperative stays, and fewer MAEs and SAEs than MLR procedures.
- Fewer procedures were needed to gain stabilization and repeatability in operating times and intraoperative blood loss levels in SLRs compared to MLR procedures.
- Operative time and intraoperative blood loss cannot be surrogates for SAE risk in MLRs, as they present significantly different learning curves.
- In MLR procedures, SAE reduction is gained significantly later than operative time and intraoperative blood loss level stabilization.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to restriction.

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

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Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist

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Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist

Klinowa resekcja brzegu wątroby wykonywana przez ginekologa onkologa w trakcie operacji cytoredukcyjnej w zaawansowanym raku jajnika jest procedurą skuteczną oraz bezpieczną

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Abstract

Objective: In this study, we aimed to determine the learning curve for liver wedge resection performed as a part of cytoreductive surgery in advanced ovarian malignant tumors. **Materials and methods:** This was a retrospective analysis of 120 women diagnosed with stage IIIC ovarian cancer according to the International Federation of Gynaecology and Obstetrics (FIGO) classification: 22 underwent liver wedge resection as a part of cytoreductive surgery (Group A), while 98 did not require liver surgery (Group B). In the study, the *t*-Student test was used for variables with normal distribution and the Mann−Whitney *U* test was utilized for increment and abnormally distributed variables. The variables categorized were shown as a number of cases (n) and a percentage (%), and compared using the chi-square test, with a p-value <0.05 being considered as significant. A cumulative sum control chart (CUSUM) method was used to investigate the learning curves in both groups and the entire cohort. **Results:** There were no significant differences in the operating time, intraoperative blood loss, postoperative hospitalization as well as in small and severe adverse effects between the Groups A and B. The operative time, total blood loss level, and incidence of adverse effects showed a similar learning curve for Group B and the entire cohort. **Conclusion:** It is safe and feasible for gynecologic oncologists to perform wedge liver resections performed as a part of cytoreductive surgery in women with advanced ovarian tumors.

Keywords: ovarian cancer, liver wedge resection, learning curve

Streszczenie

Cel: Celem pracy jest ocena krzywej uczenia się klinowej resekcji wątroby jako integralnej części operacji cytoredukcyjnej w zaawansowanym raku jajnika. **Materiał i metody:** Retrospektywna analiza objęła 120 kobiet z rozpoznaniem raka jajnika w stopniu zaawansowania IIIC według Międzynarodowej Federacji Ginekologów i Położników z roku 2018 (FIGO). Grupę A stanowiło 22 pacjentek, u których wykonano klinową resekcję wątroby; w grupie B 98 pacjentek nie wykonywano tej procedury. W analizie statystycznej wykorzystano test *t*-Studenta oraz test *U* Manna–Whitneya, jak również test chi^2 oraz metodę kontrolnego, skumulowanego wykresu sum (CSUM). Poziom istotności statystycznej ustalono jako $p < 0{,}05$. **Wyniki:** Nie stwierdzono istotnych różnic w medianach czasu zabiegu operacyjnego, śródoperacyjnej utraty krwi, czasu hospitalizacji po zabiegu, jak również w występowaniu zdarzeń niepożądanych pomiędzy Grupą A i B. Krzywe uczenia analizujące czas zabiegu, śródoperacyjną utratę krwi oraz czas hospitalizacji po zabiegu były podobne w grupie Grupy B i w całej kohorcie badanych pacjentek. **Wnioski:** Klinowa resekcja przerzutów do wątroby, wykonywana przez ginekologa onkologa, w trakcie operacji cytoredukcyjnej u kobiet z zaawansowanym rakiem jajnika jest procedurą bezpieczną i nie zwiększa ryzyka zdarzeń niepożądanych.

Słowa kluczowe: rak jajnika, klinowa resekcja wątroby, krzywa uczenia

INTRODUCTION

Malignant ovarian tumors comprise: ovarian cancers, germ-cell tumors, sex-cord tumors and metastatic tumors. Ovarian cancer accounts for up to 90% of all ovarian malignancies and is the second most common gynecologic malignancy in the developed countries, following endometrial cancer [1–4]. Contrary to endometrial cancer, however, it presents a significantly poorer prognosis [1,2]. Ovarian cancer predominately affects women in peri-menopausal age and, due to its non-patognomic symptoms, it has a rapid progression rate and there is no available screening for it. Up to 65% of ovarian cancers are stage III or IV per the International Federation of Gynaecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique; FIGO) classification at the time of diagnosis. Stage III ovarian cancer is subdivided into: (1) stage IIIA, defined as a presence of a primary gross tumor in the pelvis with cancerous cells spread in the abdominal cavity; (2) stage IIIB – in which gross cancerous tissue <2 cm is present above the pelvic rim; and (3) stage IIIC − in which gross cancerous tissue >2 cm is present above the pelvic rim and includes liver capsule involvement, but there are no parenchymal metastases [5]. Contrary to ovarian cancers, non-epithelioid ovarian malignancies affect younger women and are smaller in diameter.

Debulking surgery is the core treatment for ovarian malignancy including cancer [3,5]. This can be performed as an initial treatment and is called a primary debulking surgery (PDS) or − in cases when a PDS is not feasible − as an interval debulking surgery (IDS) done after the neoadjuvant chemotherapy. In both cases, the aim of the treatment is to achieve a complete resection of primary tumor and cancerous infiltration – R0. If that is not possible, it is accepted to remove all the macroscopic disease, but microscopic margins can be cancer-positive, which is called a R1 resection. Finally, the macroscopic residual tumor is classified as an R2 resection and significantly reduces the chance of complete recovery [6]. More than 40% of patients with stage IIIC/IV disease according to the previously-mentioned classification show widespread peritoneal carcinomatosis and require high-complexity surgery including extra-gynecologic procedures (e.g. rectosigmoid, large and small bowel, as well as diaphragmatic resection, splenectomy, and liver surgery including wedge resections to achieve R0 or R1 goals [7,8].

In this study, we aimed to evaluate the prevalence of liver involvement in women with ovarian cancer at the time of diagnosis, and to analyze the safety and feasibility of liver wage resection as a part of DS performed by a gynecologic oncologist.

MATERIAL AND METHODS

Identification of cases

We retrospectively identified 319 cases of ovarian cancer treated in our tertiary gynecologic oncology unit between the 1st of Jan 2010 to 31st of Dec 2019. The inclusion criteria for further analysis were following: (1) age 18+ years; (2) full histopathological report confirming ovarian cancer diagnosis; (3) FIGO stage IIIC disease; (4) PDS or IDS performed by a gynecologic oncologist. Patients with (1) incomplete medical records; (2) who had surgery co-performed by a colorectal, oncologic, hepatobiliary surgeon or a urologist; (3) with non-epithelioid ovarian malignancy were excluded from the study. Additionally, we identified 11 women with a history of a pelvic/abdominal surgery: 3 after laparoscopic cholecystectomy, 1 after laparoscopic appendectomy, 2 after laparoscopic supracervical hysterectomy, one after laparotomy and total hysterectomy and 8 after caesarean section. These patients were also included in the analysis to maintain the consecutiveness of cases as high as possible.

The monodisciplinary surgical team consisted of two gynecologic oncologists who performed cytoreductive surgery during the whole study period. The third member of the surgical team was under training in obstetrics and gynecology and rotated according to their residency program [9].

The endpoints analyzed were as follows: (1) operating time measured from skin incision to skin closure; (2) intraoperative blood loss level, defined as blood volume removed by suction; and (3) postoperative hospital stay length calculated from the first postoperative day to hospital discharge date. Women who had liver wage resection performed as a part of debulking surgery were enrolled to Group A, while Group B comprised patients who did not have this procedure.

Patients' safety evaluation

Patients' safety was evaluated based on the presence of adverse events, an inevitable aspect of the medical services provided, and these events were defined as minor Adverse Effects (mAEs) and severe Adverse Effects (sAEs). mAEs matched complications type I–IIIa according to the Clavien−Dindo classification [10] and included: (1) wound infection; (2) prolonged hospital stay (>10 days); and (3) hematoma managed nonsurgically. sAEs also corresponded with the Clavien−Dindo IIIb–V complications [10] and were as follows: (1) patient death; (2) admission to the intensive care unit; (3) reoperation due to intraperitoneal bleeding; (4) wound dehiscence requiring re-suturing under general anesthesia; (5) leakage of rectosigmoid colon anastomosis; (6) ureteral leakage; (7) vesico-vaginal and recto-vesical fistula.

Statistical analysis

Using the Kologomorov−Smirnoff test, the distribution of the continuous variables analyzed was checked. Data presenting normal distribution were presented as medians and standard deviation (±SD), while variables with abnormal distribution, as well increment data, were shown as means and interquartile range (IQR). The *t*-Student test was utilized for variables with normal distribution and the Mann−Whitney *U* test was selected for increment and abnormally distributed variables. Categorized variables were shown as a number of cases (n) and a percentage (%) and compared using the chi-square test.

As described in our former study, we applied the cumulative sum control chart (CUSUM) analysis to investigate the learning curve in terms of operative time, intraoperative blood loss and the length of hospital stay as well as incidence of sAEs and mAEs in women treated surgically for stage IIIC ovarian cancer [10]. As one of the investigated groups had less than 30 cases, Yate's correction was applied when appropriate.

A p value of 0.05 was considered statistically significant, and all the calculations were performed using the STATISTICA data analysis software (TIBCO Software Inc. 2017, version 13.0, Palo Alto, CA, USA).

RESULTS

Patients and procedures

From the total number of 323 identified patients with ovarian cancer, after applying the inclusion and exclusion criteria, 122 (48.61%) were identified as eligible for the study (Fig. 1). Baseline characteristics of the study cohort are shown in Tab. 1. Based on their medical records, we confirmed 22 cases of patients with liver wage resection, who were included in Group A, while Group B comprised 98 women, who did not have this procedure performed during the debulking surgery (Fig. 1).

In the entire cohort, the median operating time was 345.00 min (IQR: 195.50), the median intraoperative blood loss was 2120.00 mL (IQR: 1,422.50) and the median hospital stay was 11.00 days (IQR: 7.00). There were no significant differences between Groups A and B in the above-mentioned variables analyzed (Tab. 2). When it comes to the incidence rate of mAEs and sAEs in the entire cohort, there were 62 (51.66%) and 42 (35.00%) cases respectively. There were no significant differences in the incidence of mAEs and sAEs between the two analyzed groups (Tab. 2).

Learning curve endpoints

The median operating time in the 120 consecutive cases was 345.00 min. (IQR: 195.50). No significant differences between Group A and B were observed (Table 2). The median intraoperative blood loss in the whole cohort was 2120.00 mL (IQR: 1422.50), and similarly, Groups A and B did not differ in a significant way (Tab. 2). Again, there were no significant differences in median postoperative hospital stay between the analyzed groups, and the median postoperative hospital stay for the entire cohort was 11.00 days (IQR: 7.00) (Tab. 2).

In Group A, the CUSUM analysis of operating time indicated that procedure no. 10 was the cut-off point of gaining a stable and repeatable surgical experience; in Group B, this point was established at procedure no. 56 (Fig. 2). When the entire cohort was analyzed, it was procedure no. 53 which was identified as the cut-off point of stable and repeatable operating time (Fig. 2). Intraoperative blood loss analysis of both groups allowed us to identify cases no. 10 and no. 53 as the cut-off points of procedure stabilization. In the entire cohort, the stabilization of intraoperative blood loss was achieved at procedure no. 62 (Fig. 3). Postoperative hospital stay stabilized after procedure no. 8 and no. 56 in Groups A and B respectively; and after procedure no. 63 in the entire cohort (Fig. 4).

Patient safety

In the entire cohort, 62 (51.66%) mAEs occurred. In Group A, there were 9 (41.00%), and in Group B, 53 (54.08%) mAEs identified. When it comes to the prevalence of mAE, there was no significant difference between these two groups (Tab. 3). Additionally, 42 (35.00%) cases of sAE were reported in the entire cohort, specifically, 8 (36.36%) in Group A and 34 (34.69%) in Group B. Again, there was no statistical difference in the incidence of sAEs between the two groups (Tab. 3).

Furthermore, the CUSUM analysis of mAEs and sAEs showed that in the entire cohort, the incidence of mAEs stabilized after 53rd, and a stable decrease in sAEs was accomplished after the 61st procedure (Figure 5 and Figure 6). The stabilization of AEs was gained with the 12^{th} and 47^{th} procedure respectively for Group A, while in Group B, they stabilized with the 17^{th} and 56^{th} procedure (Figs. 5, 6).

DISCUSSION

Our findings on operating time and intraoperative blood loss during debulking surgery in advanced ovarian cancer are comparable with the findings of Nishikimi et al., proving that upper abdominal complex surgery performed by a well-trained gynecologic oncologists team is a safe and feasible procedure with optimal oncological results [11,12]. A further detailed analysis showed that liver wedge resection during a cytoreductive surgery in women with FIGO stage IIIC ovarian malignancy does not significantly impact either the operating time, intraoperative blood loss, or postoperative hospital stay. This procedure also did not impact the shape of a learning curve of the operating time, intraoperative blood loss, or postoperative hospital stay. A forward shift of several cases after that procedure stabilization was gained in the entire cohort compared to Group B was due to an increase in number of analyzed cases rather than a result of gaining surgical skills. In Group A, the learning curves of operating time, intraoperative blood loss, and postoperative hospital stay remained irregular and different in shape compared to Group B and the entire cohort.

The prevalence of mAEs and sAEs showed in our study remain comparable with other results [11,12]. Performing liver wedge resection did not increase the prevalence of mAEs or sAEs. Comparable learning curves of mAEs and sAEs in Group B and the entire cohort additionally confirm that the fact that the liver wedge resection is performed by a gynecologic oncologist does not impact the final outcome of the cytoreductive surgery in advanced ovarian cancer. These findings remain consistent with what Bacalbaşa et al. postulated based on literature review, namely, that properly performed surgical procedures involving liver in women suffering from ovarian cancer not only do not increase the risk of postoperative AEs, but also significantly increase the overall survival rate [13]. In another study, Bacalbaşa et al. concluded that resection of liver metastases in women with ovarian cancer performed as a part of a primary, secondary and even tertiary or quaternary cytoreductive surgery are beneficial in terms of survival rate and indicate that liver resection remains safe with no mortality and a 25% morbidity rate [14]. This conclusion stays in consistency with Roh et al.'s results, who analysed 4 cases of liver wedge resections, 13 cases of unisegmentectomy, and 1 bisegmentectomy as a part of a secondary cytoreductive surgery for recurrent ovarian cancer, and concluded that hepatic resection for recurrent ovarian cancer is safe and even associated with a favorable outcome and a low risk of AEs [15].

The major strength of this study is a large sample size of patients with stage IIIC ovarian cancer proven with a histopathological report and a relatively substantial number of patients who underwent liver wedge resection. We are, however, aware of its limitations. Firstly, we were unable to analyze neither the operative time of liver wedge resection, nor the intraoperative blood loss directly connected with this procedure. Based on the learning curves in Group A, these data should be interpreted with caution. Secondly, the cytoreductive surgeries were not performed by a single gynecologic oncologist, but by a team consisting of two gynecologic oncologists and a rotating third member under training in obstetrics and gynecology. Therefore, we analyzed gaining surgical experience in a debulking surgery performed due to an advanced ovarian cancer by an operating team, and not by a single surgeon.

This can be explained by the fact that a high-complexity surgery performed in women with advanced ovarian cancer, usually in combination with upper abdominal surgery, and additionally, bowel and liver resection, requires an experienced surgical team and this kind of experience can be hardly gained by a single, even highly skilled and practized surgeon, as concluded by Nishikimi et al. [13].

In conclusion, wedge liver resection performed as a part of cytoreductive surgery in women with advanced ovarian cancer can be performed safely and feasibly by gynecologic oncologists. It does not increase the risk of mAEs or sAEs, nor significantly affects operating time, intraoperative blood loss or postoperative hospital stay.

Institutional Review Board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Jagiellonian University (protocol code: 1072.6120.238.2021; date of approval: 29 September 2021).

Informed consent statement

Patient consent was waived as the study involved retrospective analysis of anonymous data.

Conflict of interest

The authors declare no conflict of interest.

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Figures

Fig. 1. Number of patients eligible to the study

Fig. 2. Cumulative sum control chart of operative (CUSUM *) operating in Group A, Group B and the entire cohort against the number of patients

Fig. 3. Cumulative sum control chart of operative (CUSUM *) intraoperating blood loss in Group A, Group B and the entire cohort against the number of patients

Fig. 4. Cumulative sum control chart of operative (CUSUM *) postoperative hospital stay in Group A, Group B and the entire cohort against the number of patients

Fig. 5. Cumulative sum control chart of operative (CUSUM *) minor Adverse Effect (mAE) in Group A, Group B and the entire cohort against the number of patients

Fig. 6. Cumulative sum control chart of operative (CUSUM *) sever Adverse Effect (sAE) in Group A, Group B and the entire cohort against the number of patients

Tab. 1. Baseline characteristics of patients

	Entire cohort (*N* = 120)	**Group A (*n* = 22)**	**Group B (*n* = 98)**	***p****
Mean age (±*SD*) [years]	57.60 (±13.03)	58.20 (±13.89)	56.31 (±11.03)	0.407
Mean BMI (±*SD*) [kg/m^2]	26.88 (±4.57)	26.80 (±4.61)	27.08 (±4.52)	0.731
Mean age at menarche (±*SD*) [years]	12.71 (±2.59)	12,92 (±1.42)	12,71 (±2.02)	0.821
Parity: • **nulliparous** • **uniparous** • **multiparous**	44 (36.66%) 12 (10.00%) 64 (53.34%)	8 (36.36%) 3 (13.64%) 11 (50.00%)	36 (36.73%) 9 (9.19%) 53 (54.08%)	0.756
Premenopausal (*n*; %) / Postmenopausal (*n*; %)	40 (33.33%) 80 (66.67%)	8 (36.36%) 14 (63.64%)	32 (32.65%) 64 (67.35%)	0.425
Mean menopausal age (±*SD*) [years]	52.54 (±8.79)	52.98 (±6.42)	51.87 (±7.92)	0.721
Tumor histology: • **high-grade serous** • **low-grade serous** • **clear cell** • **endometroid** • **mucinous**	72 (59.02%) 31 (27.68%) 5 (4.10%) 4 (2.46%) 8 (6.56%)	13 (59.10%) 4 (18.17%) 2 (9.09%) 0 (0.00%) 3 (13.64%)	59 (60.02%) 27 (27.74%) 3 (3.06%) 4 (4.08%) 5 (5.10%)	0.476
Timing of cytoreductive surgery:				

• **primary** • **interval**	82 (68.33%) 38 (31.67%)	12 (54.55%) 10 (45.45%)	72 (71.43%) 28 (28.57%)	0.088

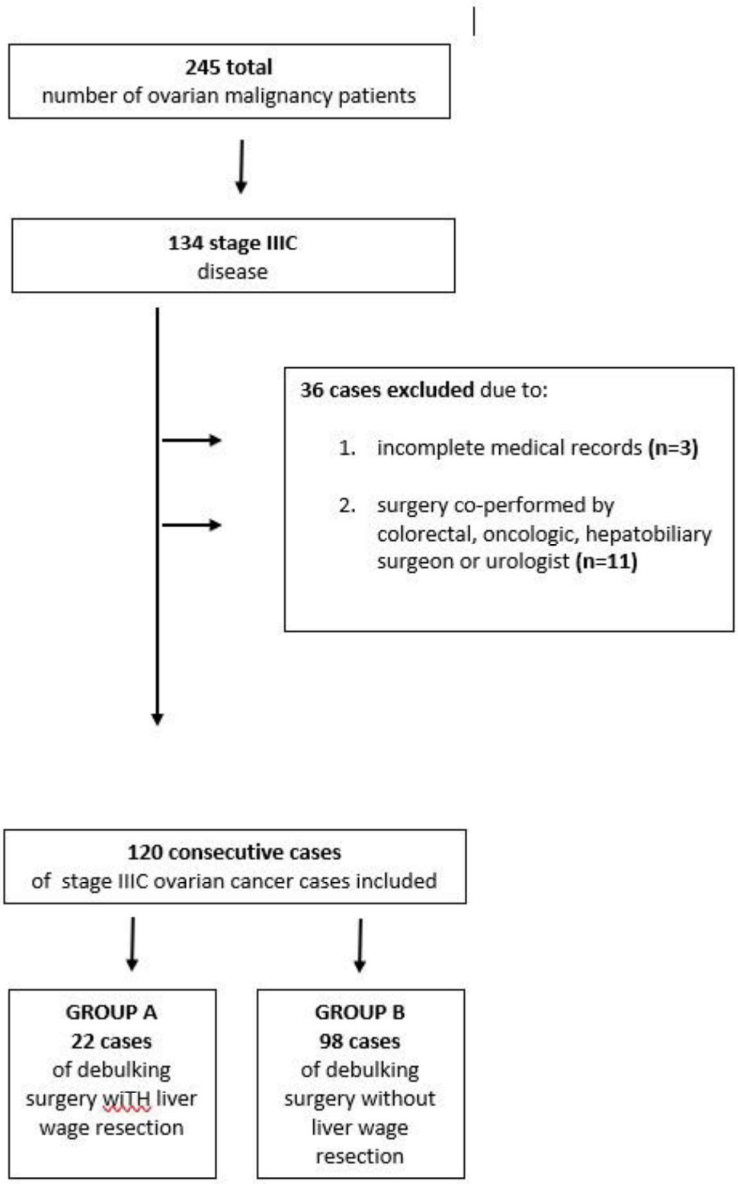
SD **–** standard deviation; **BMI –** body mass index; **IQR –** interquartile range.

* Compared between Group A and B

Tab. 2. Type of surgical procedures and outcomes

	Entire cohort (*N* = 120)	**Group A (*n* = 22)**	**Group B (*n* = 98)**	***p****
Median operating time (IQR) [min.]	345.00 (IQR: 195.50)	360.00 (IQR: 205.00)	330.00 (IQR: 195.00)	0.287
Median postoperative hospital stay (IQR) [days]	11.00 (IQR: 7.00)	10.00 (IQR: 2.50)	11.00 (IQR: 8.00)	0.194
Median intraoperative blood loss (IQR) [mL]	2,120.00 (IQR: 1,422.50)	1,805.00 (IQR: 1,660.00)	2,135.00 (IQR: 1,275.00)	0.279
Number of minor adverse effects (%)	62 (51.66%)	9 (41.00%)	53 (54.08%)	0.777
Number of severe adverse effects (%)	42 (35.00%)	8 (36.36%)	34 (34.69%)	0.882

IQR – interquartile range; *Compared between Group A and B



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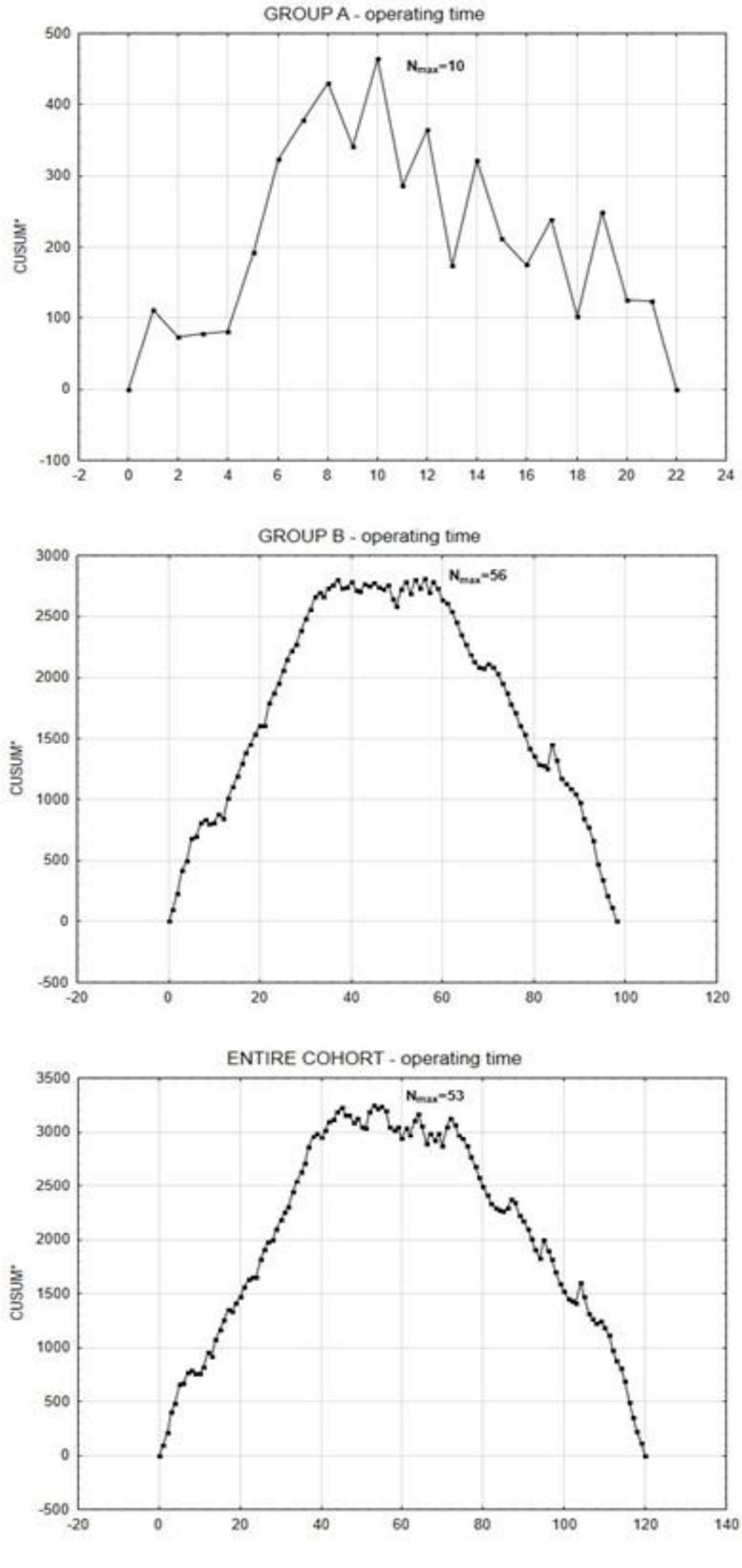

Fig. 2. Cumulative sum control chart of operative (CUSUM *) operating in Group A, Group B and the entire cohort against the number of patients

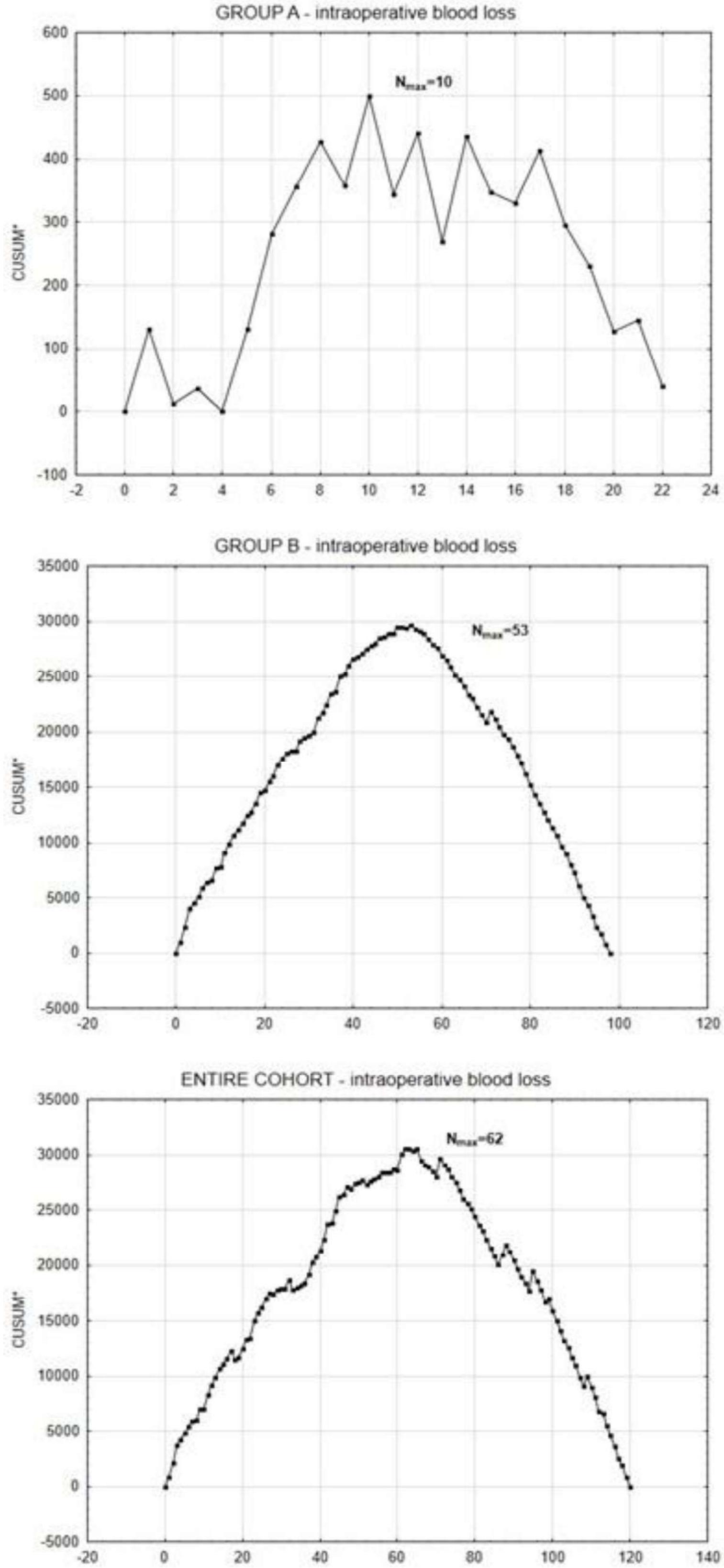

Fig. 3. Cumulative sum control chart of operative (CUSUM *) intraoperating blood loss in Group A, Group B and the entire cohort against the number of patients

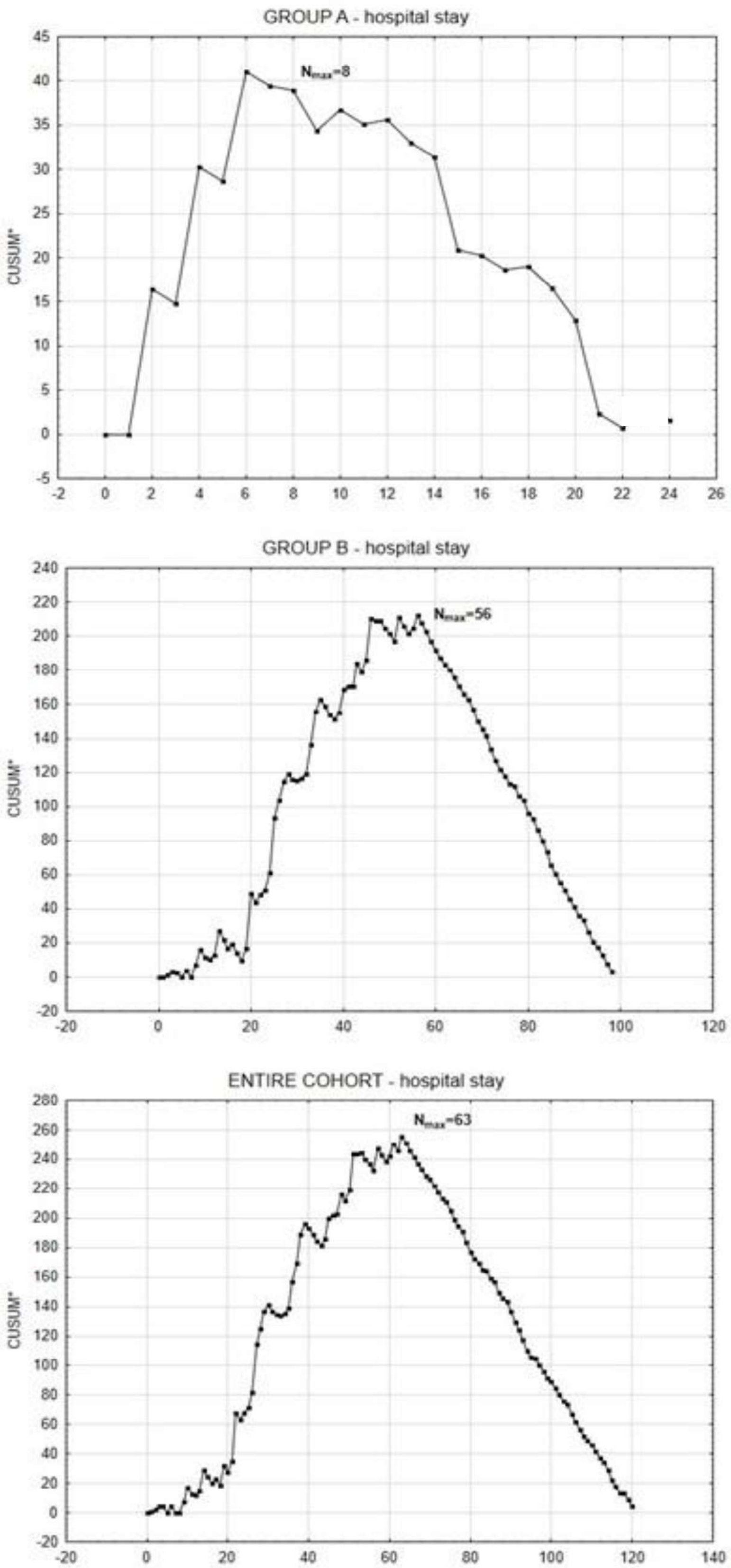

Fig. 4. Cumulative sum control chart of operative (CUSUM *) postoperative hospital stay in Group A, Group B and the entire cohort against the number of patients

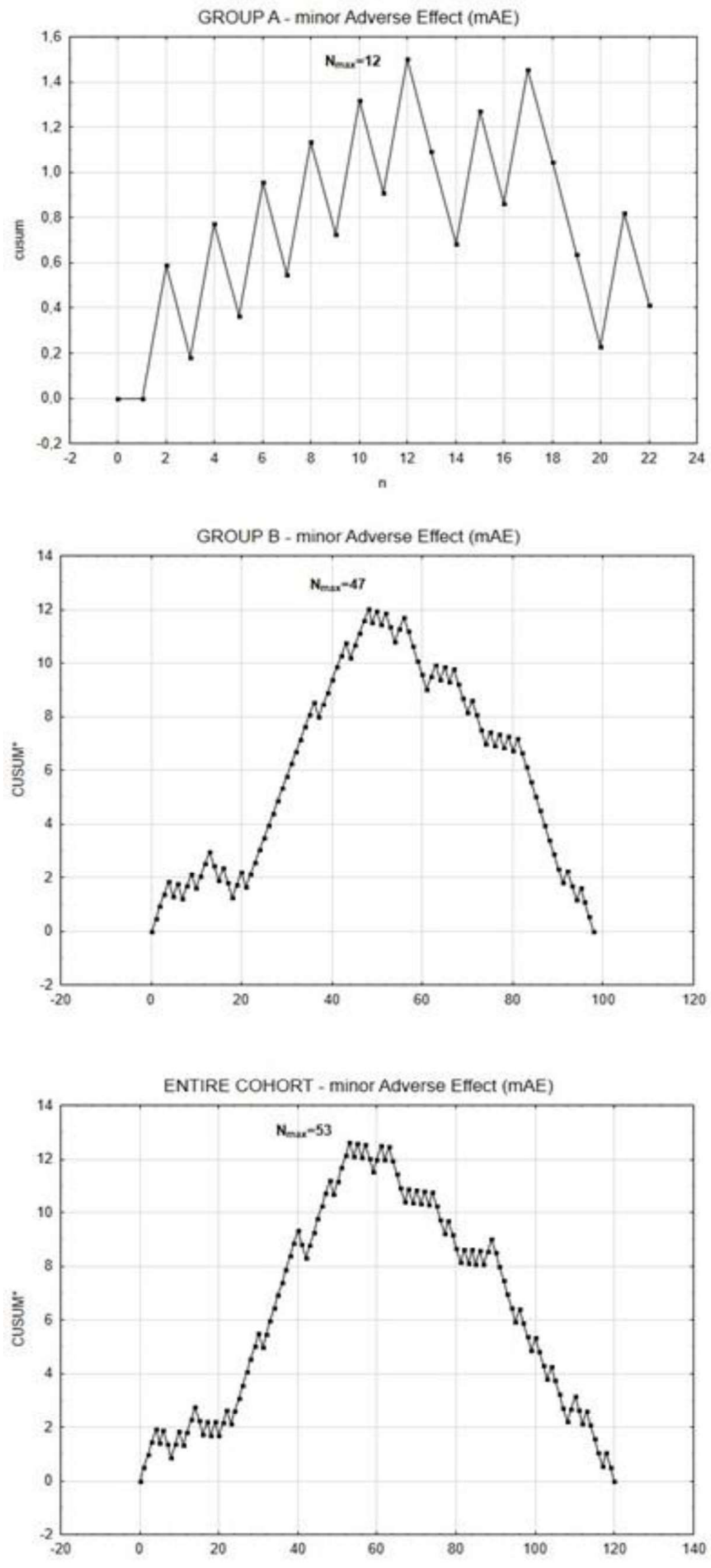

Fig. 5. Cumulative sum control chart of operative (CUSUM *) minor Adverse Effect (mAE) in Group A, Group B and the entire cohort against the number of patients

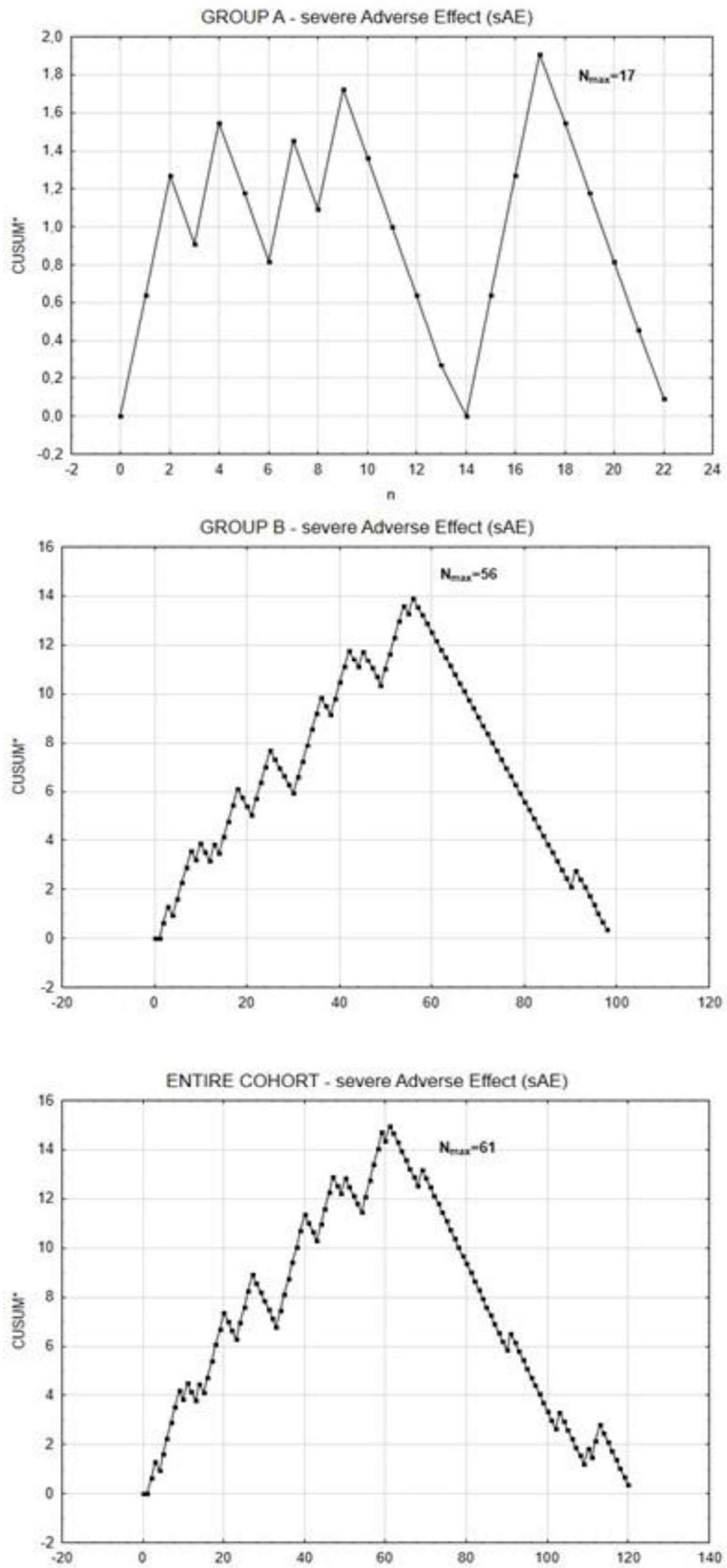

Fig. 6. Cumulative sum control chart of operative (CUSUM *) sever Adverse Effect (sAE) in Group A, Group B and the entire cohort against the number of patients

Kraków, dnia 19.04.2022.

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OŚWIADCZENIE

Jako współautor pracy pt.

"A Retrospective, Single-Centre Study on the Learning Curve for Liver Tumor Open Resection in Patients with Hepatocellular Cancers and Intrahepatic Cholagangiocarcinomas."

Banas, B.; Kolodziejczyk, P.; Czerw, A.; Banas, T.; Kotwas, A.; Richter, P. A Retrospective, Single-Centre Study on the Learning Curve for Liver Tumor Open Resection in Patients with Hepatocellular Cancers and Intrahepatic Cholagangiocarcinomas. Int. J. Environ. Res. Public Health 2022, 19, 4872. https://doi.org/10.3390/ ijerph19084872

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Banas B, Gwizdak P, Zabielska P, Kolodziejczyk P, Richter P. Learning Curve for Metastatic Liver Tumor Open Resection in Patients with Primary Colorectal Cancer: Use of the Cumulative Sum Method. Int. J. Environ. Res. Public Health 2022, 19, 1068. https://doi.org/10.3390/ ijerph19031068

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Kraków, dnia 19.04.2022.

Prof. dr hab. n. med.
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/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

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/podpis współautora/

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Piotr Kołodziejczyk
/tytuł zawodowy, imię i nazwisko/

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"Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist"

Banas B, Kolodziejczyk P, Pitynski K, Kolodziejczyk P, Mleko M, Richter P. Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist. Curr Gyn Onc. 2021; 19: w druku

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
krytyczna analiza wyników pracy, wniosków oraz analiza manuskryptu i wyniósł 15%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład **lek. Bartłomieja Banasia** przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

P. Kołodziejczyk
....
/podpis współautora/

Kraków, dnia 20.04.2022.

Prof. dr hab. n. med.
Kazimierz Pityński
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

"Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist"

Banas B, Kolodziejczyk P, Pitynski K, Kolodziejczyk P, Mleko M, Richter P. Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist. Curr Gyn Onc. 2021; 19: w druku

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
zebranie i walidacja danych, analiza wyników pracy oraz wniosków i wyniósł 5%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład **lek. Bartłomieja Banasia** przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

....
/podpis współautora/

Kraków, dnia 21.04.2022.

Lek. med. Michał Mleko
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.
"Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist"
Banas B, Kolodziejczyk P, Pitynski K, Kolodziejczyk P, Mleko M, Richter P. Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist. Curr Gyn Onc. 2021; 19: w druku

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
zebranie i współanaliza danych i wyniósł 5%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład **lek. Bartłomieja Banasia** przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

Mleko Michał
....
/podpis współautora/

Kraków, dnia 19.04.2022.

Prof. dr hab. n. med.
Piotr Richter
/tytuł zawodowy, imię i nazwisko/

OŚWIADCZENIE

Jako współautor pracy pt.

"Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist"

Banas B, Kolodziejczyk P, Pitynski K, Kolodziejczyk P, Mleko M, Richter P. Wedge liver resection as a part of cytoreductive surgery in advanced ovarian cancer being a safe and feasible procedure for a gynecologic oncologist. Curr Gyn Onc. 2021; 19: w druku

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji to:
walidacja poprawności danych oraz krytyczna recenzja manuskryptu i wyniósł 5%.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład **lek. Bartłomieja Banasia** przy opracowywaniu koncepcji, wykonywaniu części eksperymentalnej, opracowaniu i interpretacji wyników tej pracy.

....
/podpis współautora/

UNIWERSYTET JAGIELLOŃSKI W KRAKOWIE

Komisja Bioetyczna Uniwersytetu Jagiellońskiego

OPINIA

nr 1072.6120.238.2021 z dnia 29 września 2021 roku

Na zebraniu w dniu 29 września 2021 r. Komisja zapoznała się z wnioskiem z dnia 15 września 2021 r.
złożonym:
przez kierownika tematu: **prof. dr hab. med. Piotr Kołodziejczyk**
zatrudnionego **Klinika Chirurgii Ogólnej, Onkologicznej i Gastroenterologicznej I Katedra Chirurgii Ogólnej UJCM 30-688 Kraków, ul. Jakubowskiego 2**

oraz jego merytorycznym uzasadnieniem dotyczącym przeprowadzenia badania pt. „Analiza krzywej uczenia się resekcji pierwotnych i przerzutowych guzów złośliwych wątroby w aspekcie bezpieczeństwa pacjenta".

Do wniosku dołączono:

1. Protokół badania, wersja 1.0 z dnia 02.07.2021 r.
2. Oświadczenie o braku załączenia formularza informacji dla pacjenta, formularza zgody uczestnika badania, formularza o ochronie danych osobowych, wersja 1.0 z dnia 02.07.2021 r.
3. Życiorys naukowy wnioskodawcy, wersja 1.0 z dnia 02.07.2021 r.
4. Lista piśmiennictwa, wersja 1.0 z dnia 02.07.2021 r.
5. Oświadczenie o realizacji badania w ramach prac badawczych UJ/UJCM.
6. Oświadczenie, że realizowane badanie nie jest eksperymentem medycznym, wersja 1.0 z dnia 02.07.2021 r.

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanego badania - na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek przedstawienia Komisji:
- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- corocznego sprawozdania z przebiegu badania,
- raportu końcowego.

Badanie może być prowadzone do dnia 31 grudnia 2022 roku.
Skład i działanie Komisji zgodne z GCP oraz wymogami lokalnymi. Lista członków Komisji biorących udział w podjęciu uchwały stanowi załącznik do niniejszego dokumentu.

Kraków, dnia 29 września 2021 r.

Komisja Bioetyczna UJ
prof. dr hab. n. med. Dominika Dudek
przewodnicząca

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Lista członków KOMISJI BIOETYCZNEJ UJ biorących udział w podjęciu uchwały dotyczącej opinii nr **1072.6120.238.2021:**

1. Przewodnicząca: prof. dr hab. n. med. Dominika Dudek – lekarz – psychiatra ------------------------------
2. Z-ca Przewodniczącej: dr hab. Jacek Jaśtal, prof. PK – filozof ------------------------------
3. dr hab. n. med. Ewa Cichocka-Jarosz, prof. UJ – lekarz - pediatra, alergolog ------------------------------
4. prof. dr hab. n. med. Tomasz Kaczmarzyk – lekarz stomatolog, chirurg stomatolog ------------------------------
5. dr hab. n. med. Ewa Konduracka, prof. UJ – lekarz – specjalista chorób wewnętrznych, kardiolog ------------------------------
6. prof. dr hab. n. med. Piotr Major – lekarz – chirurg ogólny, chirurg onkolog ------------------------------
7. dr hab. n. med. Agnieszka Olszanecka – lekarz – specjalista chorób wewnętrznych, hipertensjolog, kardiolog ------------------------------
8. dr hab. n. med. Szymon Skoczeń – lekarz – pediatra, onkolog hematolog dziecięcy, transplantolog kliniczny ------------------------------
9. dr hab. n. med. Klaudia Stangel-Wójcikiewicz – lekarz – ginekolog-położnik ------------------------------
10. dr n. med. Stefan Bednarz – lekarz – specjalista chorób wewnętrznych, przedstawiciel Okręgowej Rady Lekarskiej w Krakowie ------------------------------
11. dr n. farm. Łukasz Hońdo – farmaceuta – specjalista farmacji klinicznej ------------------------------
12. dr Jacek Prusak – duchowny, psycholog ------------------------------
13. mgr Anna Layer-Janiga – radca prawny ------------------------------
14. Jolanta Kopeć – położna ------------------------------