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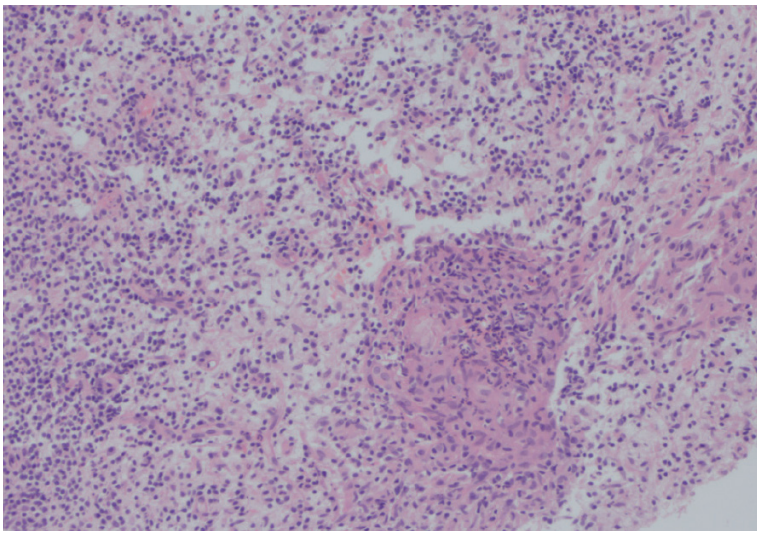

Polskie Towarzystwo Onkologiczne
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy
PTO
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Cover photo: Mixed lympho-granulocytic inflammatory infiltrate with non-necrotic granuloma. Courtesy of Andrzej Lorek

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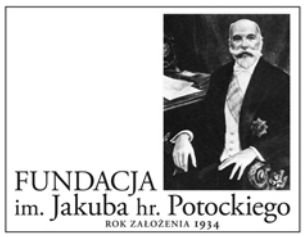

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Contents

VIA MEDICA

COVID-19

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Zalecenia dla pacjentów onkologicznych w związku z sytuacją epidemiologiczną w kraju

16 marca 2020

W związku z rozprzestrzenianiem się wirusa SARS-CoV-2 oraz mając na względzie fakt, że chorzy na nowotwory w trakcie leczenia mają często obniżoną odporność, w szpitalach wprowadzono wzmożone systemy ochrony pacjentów i personelu medycznego. Prosimy pacjentów i ich rodziny o stosowanie się do nowych procedur.

Według informacji podawanych przez Ministerstwo Zdrowia, najbardziej narażone na rozwinięcie ciężkiej postaci choroby i zgon są osoby starsze, a także z obniżoną odpornością, którym towarzyszą inne choroby, w szczególności przewlekłe. Dotyczy to również pacjentów onkologicznych.

W przypadku podejrzenia zakażenia wirusem SARS-CoV-2 wszystkim osobom zaleca się pilny kontakt pod numerem telefonu – **800 190 590** – infolinia Narodowego Funduszu Zdrowia dotycząca postępowania w sytuacji podejrzenia zakażenia koronawirusem.

Wszystkich pacjentów prosimy o stosowanie się do zaleceń ogólnych Ministra Zdrowia.

Pacjenci onkologiczni leczeni w trybie szpitalnym

1. Szpitale wprowadziły całkowity zakaz odwiedzin pacjentów onkologicznych. Zakaz obowiązuje do odwołania.
2. Pacjenci hospitalizowani mają bezwzględny zakaz opuszczania szpitali, gdyż przebywając poza szpitalem mogą zarazić się wirusem. Dotyczy to również spotkań z rodziną.
3. Personel medyczny dokłada wszelkich starań, aby pacjenci przebywający na oddziałach byli bezpieczni.

Pacjenci leczeniu w trybie ambulatoryjnym/ wizyty kontrolne

1. Pacjent przed wizytą w centrum onkologii powinien zmierzyć sobie temperaturę. Jeśli wynik pomiaru będzie równy 38 stopni C lub wyższy, występują objawy, takie jak: kaszel, duszność oraz pacjent znajduje się w grupie ryzyka (pobyt w okresie ostatnich 14 dni w rejonie aktywnej transmisji koronawirusa SARS-CoV-2 lub kontakt z osobą zakażoną) – NIE POWINIEN PRZYCHODZIĆ DO CENTRUM ONKOLOGII, ponieważ stanowi potencjalne zagrożenie dla innych pacjentów przebywających w szpitalu.
2. Pacjent, jeśli to możliwe, powinien przyjechać do szpitala sam lub w towarzystwie maksymalnie jednej osoby. Szpitale proszą o ograniczenie przychodzenia do szpitala z osobami towarzyszącymi – nie dotyczy to pacjentów, którzy potrzebują wsparcia opiekuna. Osoba towarzysząca musi być zdrowa – jej również zostanie zmierzona temperatura i zebrany wywiad medyczny.
3. Wejścia do szpitali onkologicznych mogą być ograniczone – w celu minimalizowania ryzyka szpitale zamykają wejścia do szpitali, pozostawiając tylko specjalne śluzy. Prosimy o stosowanie do informacji na drzwiach szpitali.
4. Ponadto, niektóre szpitale mogą wprowadzić zmiany w wizytach kontrolnych – zalecamy, aby zadzwonić wcześniej do szpitala i zapytać, czy planowana wizyta jest aktualna. Jeśli wizyta nie została odwołana – prosimy stosować się do ww. procedur bezpieczeństwa.
5. Pacjenci proszeni są o przychodzenie na wyznaczoną godzinę, którą mają Państwo w karcie pacjenta. Nie ma potrzeby by przychodzili Państwo wcześniej i narażali się na ryzyko infekcji.

   Apelujemy o odpowiedzialność i zrozumienie.

Informacje o zmianach w organizacji pracy centrów onkologii, dostępne są na stronach internetowych placówek:

- Narodowy Instytut Onkologii – Państwowy Instytut Badawczy w Warszawie
- Narodowy Instytut Onkologii – Państwowy Instytut Badawczy oddział w Krakowie
- Narodowy Instytut Onkologii – Państwowy Instytut Badawczy oddział w Gliwicach
- Wojskowy Instytut Medyczny w Warszawie
- Instytut Gruźlicy i Chorób Płuc w Warszawie
- Zachodniopomorskie Centrum Onkologii

- Świętokrzyskie Centrum Onkologii SP ZOZ w Kielcach
- Wielkopolskie Centrum Onkologii w Poznaniu
- Wojewódzkie Wielospecjalistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Łodzi
- Samodzielny Publiczny ZOZ MSW z Warmińsko-Mazurskim Centrum Onkologii w Olsztynie
- Kliniczny Szpital Wojewódzki nr 1 im. Fryderyka Chopina w Rzeszowie
- Szpital Specjalistyczny w Brzozowie
- Dolnośląskie Centrum Onkologii we Wrocławiu
- Centrum Onkologii w Bydgoszczy
- Uniwersyteckie Centrum Kliniczne w Gdańsku
- Szpitale Pomorskie Sp. z o.o. w Gdyni
- Beskidzkie Centrum Onkologii Szpital Miejski im. Jana Pawła II w Bielsku-Białej
- Szpital Uniwersytecki im. Karola Marcinkowskiego w Zielonej Górze
- Białostockie Centrum Onkologii im. Marii Skłodowskiej-Curie
- SP ZOZ Opolskie Centrum Onkologii w Opolu
- Centrum Onkologii Ziemi Lubelskiej w Lublinie

Zalecenia zostały opracowane na podstawie procedur wdrożonych w specjalistycznych szpitalach onkologicznych.

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Zalecenia Polskiego Towarzystwa Onkologicznego i Polskiego Towarzystwa Chirurgii Onkologicznej w sprawie postępowania z pacjentami onkologicznymi

18 marca 2020

W związku z sytuacją epidemiologiczną w kraju, Polskie Towarzystwo Onkologiczne zaleca wszystkim podmiotom medycznym zajmującym się leczeniem onkologicznym wdrożenie procedur bezpieczeństwa mających na celu ochronę przed zarażeniem wirusem SARS-CoV-2 pacjentów oraz personelu medycznego.

Przypominamy, że choroby nowotworowe nadal pozostają drugą najczęstszą przyczyną zgonów w Polsce. Śmiertelność w tej grupie chorych jest jedną z najwyższych, dlatego opieka nad pacjentami onkologicznymi powinna być bezwzględnie kontynuowana. Sytuacja epidemiologiczna nie powinna być przesłanką do całkowitego wstrzymania przyjęć pacjentów onkologicznych. Każdy pacjent ma prawo do kontynuowania terapii przeciwnowotworowej. Dotyczy to również pacjentów z podejrzeniem nowotworu – oni również nie powinni pozostać bez opieki. Obecnie najwyższym priorytetem jest zachowanie bezpieczeństwa i prawidłowości leczenia wielospecjalistycznego radykalnego leczenia chorych na nowotwory nad czym pracują rzesze lekarzy onkologów w całym kraju.

Przypominamy również o zaleceniach ogólnych dla pacjentów onkologicznych w związku z sytuacją epidemiologiczną w kraju. Prosimy o bezwzględne stosowanie się do zaostrzonych procedur bezpieczeństwa:

- Szpitale wprowadziły całkowity zakaz odwiedzin pacjentów onkologicznych. Zakaz obowiązuje do odwołania.
- Pacjenci hospitalizowani mają bezwzględny zakaz opuszczania szpitali, gdyż przebywając poza szpitalem mogą zarazić się wirusem. Dotyczy to również spotkań z rodziną.
- Prosimy o ograniczenie wizyt w szpitalach onkologicznych wyłącznie do umówionych wizyt, uprzednio zatwierdzonych przez szpital.
- Przy wejściu do szpitali onkologicznych prosimy o zachowanie bezpiecznej odległości od innych osób i stosowanie się do poleceń personelu medycznego.
- Pacjent przed wizytą w centrum onkologii powinien zmierzyć sobie temperaturę. Jeśli wynik pomiaru będzie równy 38 stopni C lub wyższy, występują objawy, takie jak: kaszel, duszność oraz pacjent znajduje się w grupie ryzyka (pobyt w okresie ostatnich 14 dni w rejonie aktywnej transmisji koronawirusa SARS-CoV-2 lub kontakt z osobą zakażoną) – NIE POWINIEN PRZYCHODZIĆ DO SZPITALA ONKOLOGICZNEGO, ponieważ stanowi potencjalne zagrożenie dla innych pacjentów przebywających w szpitali.
- W przypadku podejrzenia zarażenia wirusem SARS-CoV-2 należy zadzwonić na specjalną infolinię NFZ: 800 190 590.

Organizacja opieki onkologicznej w sytuacji epidemii

Ze względu na duże ryzyko zarażenia wirusem SARS-CoV-2 w obecnej sytuacji należy dążyć do skoordynowania opieki onkologicznej w województwach oraz sprawnej komunikacji. Nadmierne rozproszenie opieki onkologicznej spowodowało powstanie dużego chaosu informacyjnego i niemożność sprawnej pomocy niektórym pacjentom, którzy z dnia na dzień zostali pozbawieni możliwości leczenia. W każdym województwie powinna zostać powołana jedna jednostka, w której pacjent będzie mógł uzyskać wszystkie niezbędne informacje. Jednostka ta powinna wesprzeć pacjenta w zorganizowaniu i przeprowadzeniu przez ścieżkę leczenia w danym województwie. Opieka onkologiczna powinna być skoncentrowana w tych ośrodkach onkologicznych, które wdrożyły procedury bezpieczeństwa.

Potrzebna krew dla pacjentów onkologicznych

Apelujemy, aby pamiętać o konieczności zapewnienia krwi i produktów krwiopochodnych dla chorych operowanych z powodu nowotworów. Narodowe Centrum Krwiodawstwa apeluje o oddawanie krwi – do tego apelu przyłączają się chirurdzy onkologiczni i inni onkolodzy!

Rekomendowane kanały komunikacji z pacjentami

Uwaga! Ze względu na wyjątkową sytuację Polskie Towarzystwo Onkologiczne otrzymało od Prezesa Urzędu Ochrony Danych Osobowych oświadczenie o tym, że przepisy o ochronie danych osobowych nie mogą być stawiane jako przeszkoda w realizacji działań w związku z walką z koronawirusem.

1. **ONKO-INFOLINIA** w każdym województwie – w województwach, w których odbywa się pilotaż sieci onkologicznej (dolnośląskie, świętokrzyskie, podlaskie) tę rolę pełnią wojewódzkie ośrodki koordynujące. Jest to najczęściej wybierany przez pacjentów kanał komunikacji. Powinien być uruchomiony w każdym województwie i obsługiwany przez osoby znające strukturę opieki onkologicznej w danym województwie (znajomość wszystkich podmiotów zajmujących się leczeniem onkologicznym, znajomość zasad systemu opieki zdrowotnej, itp.). Ze względu na duże obciążenie konsultantów należy uruchomić też alternatywne kanały komunikacji.
2. **Kontakt SMS** – wykorzystanie istniejących bramek SMS.
3. **Kontakt E-MAIL** – wykorzystanie istniejących, sprawdzonych adresów mailowych.
4. **Kontrakt za pośrednictwem platform internetowych** – wykorzystanie istniejących szpitalnych platform do komunikacji z pacjentami.
5. **Telekonsultacja** – w przypadku podejrzenia jakiegokolwiek ryzyka zakażenia zaleca się przeprowadzenie telekonsultacji.

Uwaga! Infolinie i bramki SMS są bardzo przeładowane co wymagać będzie dłuższego czasu na wygenerowanie odpowiedzi. Jednak są to obecnie najbezpieczniejsze formy komunikacji. Prosimy pacjentów o cierpliwość i wyrozumiałość.

Rekomendowane postępowanie z pacjentami onkologicznymi

1.1. Pacjenci rozpoczynający terapię onkologiczną – z kartą DiLO

Pacjenci z podejrzeniem nowotworu z wystawioną kartą DiLO, którzy chcą umówić się na wizytę, powinni skorzystać z kontaktu telefonicznego lub za pośrednictwem innych dostępnych w danym szpitalu kanałów komunikacji (SMS, wewnętrzny system informatyczny dla pacjentów). Szpital po ustaleniu terminu wizyty powinien skontaktować się z pacjentem.

1.2. Pacjenci rozpoczynający terapię onkologiczną – bez karty DiLO

W przypadku, gdy pacjent ma podejrzenie nowotworu, ale nie ma karty DiLO, istnieje możliwość zdalnego wystawienia karty przez lekarza POZ/AOS lub punkt rejestracji w szpitalu onkologicznym. Pacjent musi jedynie znać NUMER tej karty. Numer karty należy podać przy umawianiu się na pierwszą wizytę w poradni onkologicznej.

1.3. Pacjenci w trakcie terapii onkologicznej

Koordynator leczenia powinien pozostać z pacjentem w stałym kontakcie telefoniczym/SMS-owym/mailowym w zakresie:

- umawiania wizyt i terminów konsultacji,
- odbierania i informowania o wynikach pacjenta,
- ustalenia terminów konsyliów,
- wyjaśnienie bieżących problemów – informacje celowane.

Zaleca się odbiór wyników badań on-line lub w specjalnie do tego przeznaczonych punktach.

1.4. Pacjenci po zakończonym leczeniu (1–5 lat)

Zaleca się uprzedni kontakt telefoniczny/mailowy.

Schemat badań kontrolnych powinien być zgodny z ustaloną ścieżkę terapeutyczną i ustalonymi terminami.

Umówione wizyty kontrolne tylko po wykluczeniu ryzyka. Pacjent powinien poddać się procedurom epidemiologicznym / przejść przez śluzę (wydzielone wejścia do szpitali/kontenery lub namioty przed szpitalami).

W przypadku podejrzenia jakiegokolwiek ryzyka zaleca się telekonsultację.

1.5. Pacjenci po zakończonym leczeniu (powyżej 5 lat)

Zaleca się kontakt telefoniczny i mailowy.

Przy kontakcie osobistym w rejestracji pacjent powinien poddać się procedurom epidemiologicznym/ i przejść przez śluzę.

Badania kontrolne w dłuższym okresie po zakończeniu leczenia nowotworów w chwili obecnej powinny być realizowane poza ośrodkami onkologicznymi i/lub ewentualnie w formie telekonsultacji.

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Stanowisko Polskiego Towarzystwa Chirurgii Onkologicznej w sprawie postępowania u chorych na nowotwory wymagających leczenia chirurgicznego w okresie zagrożenia epidemiologicznego

25 marca 2020

Zarząd Polskiego Towarzystwa Chirurgii Onkologicznej zdecydowanie wzywa do ścisłego przestrzegania wprowadzanych regulacji prawnych dotyczących funkcjonowania całego kraju w okresie stanu epidemicznego oraz zasad opracowanych przez World Health Organization i Ministerstwo Zdrowia (www.mz.gov.pl). Powinnością lekarzy jest m.in. wskazywanie właściwych zachowań w sytuacji zagrożenia zdrowia publicznego.

Jednocześnie Zarząd PTChO wzywa chirurgów onkologów do stosowania środków ochrony osobistej zgodnie z zaleceniami szpitali i troski o własne zdrowie, bowiem zdrowie lekarzy jest niezbędnym warunkiem, aby mogli oni pomagać pacjentom.

Polskie Towarzystwo Chirurgii Onkologicznej apeluje do wszystkich chirurgów zajmujących się leczeniem chorych na nowotwory o zapoznanie się z rekomendacjami Polskiego Towarzystwa Onkologicznego i Polskiego Towarzystwa Chirurgii Onkologicznej, które są dostępne m.in. na stronach obu Towarzystw (www.ptomed.pl; www.ptcho.pl). Apelujemy także, aby wszyscy chirurdzy onkologiczni zapoznali się ze stanowiskiem Polskiego Towarzystwa Onkologii Klinicznej, dostępnym na stronie www.ptok.pl oraz udostępnionymi przez Polską Ligę Walki z Rakiem zaleceniami włoskich towarzystw onkologicznych (www.ligawalkizrakiem.pl).

Odnośnie do chirurgicznego postępowania terapeutycznego, podkreślamy, iż utrzymanie ciągłości wielospecjalistycznego leczenia chorych na nowotwory jest kluczowe dla efektu terapii, z tego powodu utrzymanie normalnej pracy oddziałów chirurgii onkologicznej winno być priorytetem dla władz. Apelujemy do władz szpitali, aby w trudnym okresie umożliwić chorym na nowotwory możliwość prawidłowej diagnostyki i leczenia z intencją radykalności.

W szczególności rekomendujemy, aby:

- We wszystkich przypadkach, w których jest to możliwe, ograniczać czas trwania pobytu w szpitalu – skrócenie czasu ekspozycji zmniejsza ryzyko transmisji zakażenia.
- Należy utrzymać wewnątrzszpitalne procedury ERAS lub podobne, bowiem pozwalają one na szybką mobilizację i wypisane chorego.
- Należy chorym w trakcie diagnostyki, leczonym oraz wypisywanym umożliwić łatwy i pewny telefoniczny całodobowy kontakt z lekarzem prowadzącym lub lekarzem dyżurnym danego oddziału (np. numer telefonu do dyżurki lekarskiej).
- Wszystkie wizyty pooperacyjne powinny odbywać się w formie teleporady, z wyjątkiem oczywistych sytuacji, w których wizyta w poradni jest nieunikniona (np. usunięcie szwów czy drenów).
- Należy zabronić zgłaszania się chorym bezpośrednio na oddział chirurgii onkologicznej celem zasięgnięcia porady, odebrania dokumentacji itp.; dopuszczalne są jedynie wizyty w poradni w przypadkach, w których jest taka bezwzględna konieczność.
- Należy odwołać wszystkie wizyty kontrolne do czasu przywrócenia normalnej pracy szpitali (z wyjątkiem chorych, u których w czasie teleporady podjęto podejrzenie nawrotu lub rozwinięcia się powikłania po leczeniu); należy także odroczyć wizyty związane z badaniami przesiewowymi.
- Należy umożliwić normalną diagnostykę i leczenie chorym z podejrzeniem lub potwierdzeniem nowotworu złośliwego.

Jednocześnie Polskie Towarzystwo Chirurgii Onkologicznej rekomenduje okresowe zapoznawanie się ze stroną internetową amerykańskiego Society of Surgical Oncology (www.surgonc.org), na której regularnie aktualizowane są swoiste narządowo rekomendacje dotyczące możliwości odroczenia

leczenia poszczególnych typów nowotworów i właściwego doboru pacjentów w przypadku wystąpienia ograniczeń w dostępności do leczenia operacyjnego. Zalecenia te opracowano w taki sposób, aby ustalone priorytety leczenia nie powodowały rzeczywistych negatywnych skutków zdrowotnych dla wszystkich pacjentów.

Wojciech Wysocki (Prezes) oraz Członkowie Zarządu Polskiego Towarzystwa Chirurgii Onkologicznej: Józef Kładny, Dawid Murawa, Piotr Rutkowski, Zbigniew I. Nowecki, Arkadiusz Jeziorski, Michał Jankowski, Jacek Kargul, Andrzej Kurylcio, Piotr Richter, Andrzej Rutkowski, Wojciech Zegarski

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Leczenie systemowe pacjentów z rozpoznaniem choroby nowotworowej w kontekście pandemii SARS-CoV-2 – stanowisko Polskiego Towarzystwa Onkologii Klinicznej

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Wstęp

Pandemia SARS-CoV-2 stała się faktem i z dnia na dzień odnotowuje się w Europie rosnącą liczbę osób zarażonych i zmarłych z powodu COVID-19. Gwałtownie narastające obciążenie systemów opieki zdrowotnej może się w niedługim czasie okazać niemożliwym do udźwignięcia nawet dla tych najlepiej zorganizowanych i finansowanych. Nie ulega wątpliwości, że w Polsce – podobnie jak we wszystkich krajach – istnieje wiele niewiadomych dotyczących zarówno czasu trwania pandemii, dynamiki przyrostu liczby chorych wymagających hospitalizacji lub intensywnej terapii, jak i możliwości organizacyjnego zabezpieczenia gwałtownie rosnących potrzeb opieki zdrowotnej. W ostatnich dniach wiele szpitali w naszym kraju zostało zamienionych w tak zwane jednoimienne szpitale zakaźne, co spowodowało *de facto* ich zamknięcie dla chorych z innymi chorobami niż COVID-19. W licznych szpitalach odwołano planowe przyjęcia i zawieszono funkcjonowanie poradni z powodu ograniczonej liczby personelu. W przypadku wielu chorób opóźnienie diagnostyki lub leczenia nie ma istotnego wpływu na rokowanie chorych, jednak nie dotyczy to chorych onkologicznych, którzy wymagają przeciwnowotworowego leczenia systemowego. W ostatnich dniach pojawiły się doniesienia medialne o zamykaniu oddziałów onkologii klinicznej w przekształcanych szpitalach lub przerywaniu leczenia systemowego z powodu panującej pandemii. Dla wielu chorych takie postępowanie może być równoznaczne z odebraniem szans na wyleczenie czy z gwałtownym pogorszeniem rokowania. W związku z powyższym oraz w odpowiedzi na wiele pojawiających się pytań dotyczących zasad postępowania z chorymi poddawanymi przeciwnowotworowemu leczeniu systemowemu w aktualnej sytuacji zagrożenia epidemicznego, Polskie Towarzystwo Onkologii Klinicznej (PTOK) przygotowało niniejsze stanowisko. Pragniemy jednocześnie zaznaczyć, że nie dotyczy ono pacjentów onkohematologicznych oraz pediatrycznych.

COVID-19 u dorosłych chorych na lite nowotwory złośliwe

Do powszechnej wiedzy należy już fakt, że populacją najbardziej narażoną na powikłania i śmierć w wyniku zarażenia SARS-CoV-2 są osoby w podeszłym wieku z chorobami współistniejącymi [1]. Ponieważ większość (>60%) przypadków nowotworów rozpoznaje się po 65. roku życia, a w Polsce obecnie żyje około miliona osób z rozpoznaniem choroby nowotworowej (w tym duża grupa jest w trakcie aktywnego leczenia), nie ulega wątpliwości, że jest to populacja szczególnego ryzyka. Dostępne informacje dotyczące przebiegu COVID-19 u chorych na nowotwory są bardzo ograniczone i dotyczą jedynie 18 przypadków [2]. Liang i wsp. [2] przeanali

zowali dane 1590 chorych na COVID-19 – w ocenianej grupie 18 (1%) miało wywiad choroby nowotworowej i odsetek ten był ponad 3-krotnie wyższy niż wskaźnik w ogólnej populacji chińskiej (0,29%). Większość chorych objętych analizą stanowiły osoby poddane obserwacji po zakończonym leczeniu przeciwnowotworowym, natomiast 6 chorych było poddawanych aktywnemu leczeniu systemowemu (2 – leczeniu celowanemu w raku płuca, 2 – chemioterapii w raku płuca, 1 – immunoterapii w raku jasnokomórkowym nerki, 1 – uzupełniającemu leczeniu systemowemu w raku piersi bez sprecyzowania rodzaju). Poważne powikłania związane z COVID-19 obserwowano zdecydowanie częściej w grupie chorych na nowotwory niż w ogólnej populacji (39% *vs.* 8%), jednak chorzy na nowotwory byli starsi (średnia wieku – 63,1 *vs.* 48,7 lat) i częściej byli palaczami (22% *vs.* 7%). W przypadku chorych na raka płuca, których w ciągu miesiąca przed rozpoznaniem COVID-19 poddano chemioterapii lub leczeniu chirurgicznemu, poważne powikłania występowały częściej niż u osób pozostających w wieloletniej obserwacji (odpowiednio – 75% *vs.* 43%). W modelu regresji logistycznej wykazano, że ryzyko wystąpienia poważnych powikłań COVID-19 było większe dla osób z wywiadem onkologicznym [iloraz szans (*odds ratio* – OR) = 5,39] niż z przewlekłą obturacyjną chorobą płuc (OR = 3,39), cukrzycą (OR = 2,2) i nadciśnieniem tętniczym (OR = 1,87). Z punktu widzenia onkologii klinicznej ważną obserwacją jest brak poważnych powikłań u większości analizowanych chorych z rozpoznaniem COVID-19 w trakcie prowadzenia przeciwnowotworowego leczenia systemowego – nie obserwowano ich ani u jedynej chorej (52 lata) leczonej z powodu raka piersi, ani u 3 chorych leczonych z powodu raka płuca (chorzy w wieku 55 i 58 lat poddawani leczeniu celowanemu; 47-letni chory poddawany chemioterapii). Poważne powikłania obserwowano u 63-letniego chorego otrzymującego paliatywną chemioterapię z powodu raka płuca i, co może być zaskakujące, u 58-letniego chorego poddawanego immunoterapii z powodu raka jasnokomórkowego nerki [2].

Niewielka liczebność analizowanej populacji nie pozwala wyciągnąć definitywnych wniosków dotyczących zasad postępowania u chorych z rozpoznaniem choroby nowotworowej w kontekście ryzyka zarażenia SARS-CoV-2. Nie ulega jednak wątpliwości, że wiek chorych, choroby współistniejące oraz leczenie przeciwnowotworowe mogą zwiększać ryzyko wystąpienia ciężkich powikłań i śmierci w przebiegu COVID-19.

W związku z powyższym, w zależności od stanu ogólnego chorego, charakteru planowanego lub prowadzonego już leczenia przeciwnowotworowego oraz stanu zaawansowania choroby, należy różnicować zasady postępowania w okresie pandemii SARS-CoV-2.

Zalecenia dotyczące systemowego leczenia onkologicznego

Leczenie systemowe chorych z rozpoznaniem choroby nowotworowej może mieć charakter radykalny (leczenie przedoperacyjne lub pooperacyjne, samodzielna chemioterapia w przypadku nowotworów chemiowyleczalnych, chemioterapia w skojarzeniu z napromienianiem) lub paliatywny. Autorzy uważają, że należy bezwzględnie dążyć do utrzymania rekomendowanej intensywności leczenia o założeniu radykalnym. Każdorazowo, w przypadku braku możliwości kontynuacji stosowanego już leczenia systemowego o założeniu radykalnym, chory musi być w trybie pilnym przekazany do innego, funkcjonującego ośrodka onkologii klinicznej w danym województwie w celu kontynuacji leczenia. Spisami takich ośrodków dysponują wojewódzcy konsultanci do spraw onkologii klinicznej.

Leczenie przedoperacyjne

Decyzja o rozpoczęciu leczenia przedoperacyjnego, podejmowana w ramach konsylium wielodyscyplinarnego, uwzględnia każdorazowo planowany termin przeprowadzenia zabiegu operacyjnego. W przypadku chorych na raka piersi, gdy celem leczenia przedoperacyjnego ma być przeprowadzenie zabiegu oszczędzającego (szczególnie u chorych po menopauzie [3]), można rozważyć kilkutygodniowe odroczenie rozpoczęcia chemioterapii przedoperacyjnej. U chorych pierwotnie operacyjnych, u których chemioterapia przedoperacyjna nie ma udowodnionego wpływu na poprawę rokowania, należy w pierwszej kolejności przeprowadzić zabieg operacyjny, a następnie zastosować systemowe leczenie uzupełniające. Z kolei u wszystkich chorych ze znacznym miejscowym zaawansowaniem choroby, gdy celem leczenia neoadiuwantowego jest osiągnięcie możliwości przeprowadzenia zabiegu chirurgicznego lub radykalnej radioterapii, postępowanie powinno być rozpoczęte bez zbędnej zwłoki. U chorych w trakcie chemioterapii przedoperacyjnej, w przypadku spodziewanego znacznego (wielotygodniowego) opóźnienia momentu przeprowadzenia zabiegu operacyjnego, należy rozważyć podanie 1–2 dodatkowych cykli chemioterapii według ostatnio stosowanego schematu. Należy przy tym upewnić się, że nie występują bezwzględne przeciwwskazania do kontynuowania chemioterapii (dotychczasowa tolerancja, kumulacyjna toksyczność). W przypadku wątpliwości związanych z ewentualnym „przedłużeniem" leczenia przedoperacyjnego istnieje możliwość konsultacji z zespołem konsultantów Kliniki Onkologii Uniwersytetu Jagiellońskiego – *Collegium Medicum* w Krakowie (chemioterapia@su.krakow.pl).

Leczenie pooperacyjne

Rozpoczęcie systemowego leczenia uzupełniającego może być w większości przypadków odroczone i podjęte w okresie do 3 miesięcy od zabiegu. Wyjątkiem są tutaj chorzy należący do grupy bardzo wysokiego ryzyka nawrotu (np. znaczne miejscowe zaawansowanie, potrójnie ujemny rak piersi). W uzasadnionych sytuacjach klinicznych leczenie uzupełniające może być zastąpione ścisłą obserwacją. W przypadku chorych na hormonozależnego raka piersi [szczególnie z niskim stopniem

złośliwości (G1) i/lub niskim indeksem proliferacyjnym (Ki67 < 30%)], u których potencjalna korzyść z chemioterapii może być niewielka, należy rozważyć samodzielną hormonoterapię uzupełniającą. W przypadku wątpliwości odnośnie możliwości/zasadności rezygnacji z uzupełniającej chemioterapii istnieje możliwość konsultacji chorych z zespołem konsultującym Kliniki Onkologii Uniwersytetu Jagiellońskiego – *Collegium Medicum* w Krakowie (chemioterapia@su.krakow.pl).

Leczenie o założeniu paliatywnym

W odróżnieniu od leczenia o założeniu radykalnym, paliatywne leczenie systemowe, szczególnie na etapie późniejszych linii, jest – w wielu przypadkach – postępowaniem o mniejszej sile dowodów naukowych uzyskanych w ramach dużych badań klinicznych z randomizacją lub metaanaliz. Jest to postępowanie oparte przede wszystkim na dostępnych i aktywnych w danym wskazaniu lekach cytotoksycznych stosowanych samodzielnie lub w schematach skojarzonych. W większości przypadków sposób prowadzenia długotrwałego, wieloetapowego leczenia paliatywnego jest konsekwencją dostępnych danych literaturowych o relatywnie niskiej wiarygodności naukowej oraz doświadczeń własnych poszczególnych ośrodków onkologicznych. Z uwagi na nieokreślony czas i zasięg pandemii SARS-CoV-2 nie ma obecnie żadnych możliwości przewidywania, jak długo konieczne będzie wdrażanie wyjątkowych zasad postępowania w przypadku chorych onkologicznych. W tym kontekście najwięcej pytań dotyczących optymalnego postępowania pojawia się w przypadku chorych wymagających przewlekłego leczenia przeciwnowotworowego. Nie ulega wątpliwości, że długotrwałe wstrzymanie systemowego leczenia zwiększa ryzyko progresji choroby, której konsekwencją może być znaczące pogorszenie stanu sprawności i wydolności narządowej chorych. Należy zatem mieć świadomość, że długotrwałe pogorszenie opieki onkologicznej nad chorymi w czasie pandemii może znacząco, w stopniu niedającym się w obecnej chwili przewidzieć, pogorszyć ich rokowanie.

W związku z powyższym, stanowisko PTOK dotyczące modyfikacji leczenia paliatywnego, w sytuacji całkowitej niepewności co do skali i czasu trwania zagrożenia epidemicznego, stanowi próbę znalezienia optymalnych rozwiązań, pozwalających w wielomiesięcznej perspektywie zapewnić maksymalne, możliwe do uzyskania bezpieczeństwo chorego i kontrolę choroby.

Proponujemy poniższe rozwiązania:

- chorzy bezobjawowi, z dobrą kontrolą choroby oraz bez zagrożenia „kryzą" narządową – należy rozważyć możliwość przerwania („wakacje terapeutyczne"), zredukowania intensywności terapii (wydłużenie odstępów pomiędzy kursami o 50–100%) lub wdrożenia leczenia systemowego z wykorzystaniem dostępnych leków doustnych (w tym stosowanych metronomicznie);
- chorzy z głęboką remisją choroby w trakcie leczenia podtrzymującego – należy rozważyć okresowe przerwanie leczenia;
- chorzy wymagający utrzymania ciągłego leczenia systemowego (zagrożenie „kryzą" narządową, objawy, niedawno rozpoczęte leczenie)
  - otrzymujący chemioterapię opartą na schematach stosowanych w odstępach 3-tygodniowych – należy kontynuować leczenie wybranym schematem,
  - otrzymujący schematy cotygodniowe – rekomenduje się modyfikację schematu do schematów 2- lub 3-tygodniowych (zwiększenie dawki leku) lub modyfikację do schematu 2-lekowego stosowanego co 2–3 tygodnie. Przykłady modyfikacji schematów cotygodniowych zostały przedstawione w tabeli I.

W przypadku wątpliwości w kwestii możliwości modyfikacji dawkowania możliwy jest kontakt z zespołem konsultującym Kliniki Onkologii Uniwersytetu Jagiellońskiego – *Collegium Medicum w Krakowie* (chemioterapia@su.krakow.pl).

Gorączka neutropeniczna w przebiegu leczenia przeciwnowotworowego

Z uwagi na fakt, że objawowa infekcja SARS-CoV-2 przebiega z wysoką gorączką, bez wykonania badań diagnostycznych

Tabela I. Przykładowe modyfikacje schematów chemioterapii w leczeniu paliatywnym

Schemat	Proponowana modyfikacja
Paklitaksel 80 mg/m^2 co tydzień	Paklitaksel 120 mg/m^2 co 2 tygodnie [4]
Gemcytabina 1000 mg/m^2 d. 1., 8. co 21 dni Gemcytabina 1000 mg/m^2 d. 1., 8. ,15. co 28 dni	Gemcytabina 1250 mg/m^2 co 2 tygodnie *Przy problemie we wcześniejszym utrzymaniu dawkowania z powodu toksyczności – gemcytabina 1000 mg/m^2 co 2 tygodnie*
Cisplatyna 25–30 mg/m^2 co tydzień	Cisplatyna 50 mg/m^2 co 2 tygodnie Cisplatyna 75 mg/m^2 co 3 tygodnie
Cisplatyna 25 mg/m^2 + gemcytabina 1000 mg/m^2 d. 1., 8. co 21 dni	Cisplatyna 50 mg/m^2 + gemcytabina 1250 mg/m^2 co 2 tygodnie
Winorelbina 25 mg/m^2 *i.v.* lub 60–80 mg/m^2 po co tydzień	50 mg p.o. (poniedziałek, środa, piątek) [5] lub 30 mg p.o. co 2. dzień (u chorych w podeszłym wieku) – cykle co 2–3 tygodnie [6]
Karboplatyna 2 AUC *i.v.* co tydzień	Karboplatyna 6 AUC *i.v.* co 3 tygodnie
Kapecytabina – dawkowanie d. 1.–14. co 21 dni	Kapecytabina – tryb ciągły (66% standardowej dawki dobowej dla cyklu 14/21), wizyty co 6 tygodni

trudno odróżnić pierwsze objawy COVID-19 od gorączki neutropenicznej. Zgodnie z aktualnymi zaleceniami, chorzy z podejrzeniem COVID-19 (co najmniej jeden z objawów: **gorączka**, kaszel, duszność) powinni być izolowani w odpowiednio wyposażonych pomieszczeniach (śluza, środki ochrony osobistej, pulsoksymetr, termometr, dostęp do gazów medycznych, zestaw do resuscytacji), a następnie poddani dalszej diagnostyce [7]. Nie ulega wątpliwości, że każdy pacjent z objawami sugerującymi COVID-19 (również chory wyłącznie z „klasyczną" gorączką neutropeniczną) może w obecnej sytuacji poważnie zaburzyć funkcjonowanie całej jednostki leczniczej i zdezorganizować pracę personelu medycznego. W związku z powyższym, w celu maksymalnego ograniczenia ryzyka występowania gorączek neutropenicznych u chorych poddawanych chemioterapii zaleca się, na czas trwania pandemii SARS-CoV-2, profilaktyczne stosowanie czynników wzrostu G-CSF u:

- wszystkich chorych otrzymujących chemioterapię z grupy pośredniego (10–20%) ryzyka występowania gorączki neutropenicznej;
- wszystkich chorych otrzymujących chemioterapię, u których obserwowano w trakcie aktualnie stosowanego schematu epizod neutropenii G3 według *Common Terminology Criteria for Adverse Events* (CTCAE) (<1000/mm^3).

Podsumowanie

Stanowisko PTOK i skrótowe zalecenia (Tab. II), wobec braku adekwatnych, silnych dowodów naukowych dla postępowania w obliczu pandemii SARS-CoV-2, stanowi odzwierciedlenie opinii autorów niniejszego opracowania. Stanowisko PTOK oraz pomoc oferowana przez zespół konsultacyjny Kliniki Onkologii Uniwersytetu Jagiellońskiego – Collegium Medicum w Krakowie mają na celu wsparcie decyzyjne onkologów klinicznych w tej ekstremalnie skomplikowanej sytuacji, w której się znaleźli.

Jako lekarze musimy pamiętać, że bezpieczeństwo nasze i naszych współpracowników jest krytycznym czynnikiem warunkującym możliwość zapewnienia ciągłej opieki naszym chorym. Jako onkolodzy kliniczni, pełniący w wielu przypadkach funkcję koordynującą i spajającą leczenie onkologiczne, możemy być zmuszeni w tej nadzwyczajnej sytuacji do nadzwyczajnych decyzji, nadzwyczajnego zaangażowania, nadzwyczajnego wysiłku. Musimy przy tym pamiętać, że w naszych rękach są zarówno losy chorych, u których nie możemy zaprzepaścić szans na całkowite wyleczenie, jak i chorych z chorobą zaawansowaną, u których nie powinniśmy naszymi decyzjami pogarszać rokowania.

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Tabela II. Zalecenia PTOK w kontekście pandemii SARS-CoV-2 – podsumowanie

1. Zalecenia postępowania w zakresie przeciwnowotworowego leczenia systemowego w okresie pandemii SARS-CoV-2 nie są oparte na wynikach prospektywnych badań i w największym stopniu uwzględniają obserwacje dotyczące postępowania w innych zakażeniach oraz opinie ekspertów.
2. Najważniejszym elementem postępowania jest przeciwdziałanie szerzeniu się zakażenia według typowych zasad zalecanych w sytuacjach zagrożenia epidemicznego.
3. Systemowe leczenie przeciwnowotworowe powinno być prowadzone według ogólnie przyjętych zasad.
4. Prowadzenie leczenia systemowego według ogólnie przyjętych zasad powinno również obejmować postępowanie w przypadku występowania powikłań.
5. Prowadzenie leczenia systemowego według ogólnie przyjętych zasad powinno być szczególnie przestrzegane w przypadku postępowania o założeniu radykalnym.
6. Przerywanie lub zaniechanie kontynuowania systemowego leczenia o założeniu radykalnym w sytuacji pandemii SARS-CoV-2 nie ma naukowego uzasadnienia.
7. Rozpoczynanie systemowego leczenia uzupełniającego może być w ściśle uzasadnionych sytuacjach klinicznych zastąpione ścisłą obserwacją. Należy rozważyć stosowanie jednej spośród możliwych do wykorzystania metod lub skrócenie długości całego leczenia.
8. Postępowanie w ramach systemowego leczenia przeciwnowotworowego o założeniu paliatywnym powinno być kontynuowane, przy czym możliwe jest modyfikowanie schematów i dawek w zależności od indywidualnych sytuacji.
9. Modyfikowanie systemowego leczenia przeciwnowotworowego stosowanego z założeniem paliatywnym może obejmować szersze korzystanie z leków w postaciach doustnych lub wykorzystanie leczenia metronomicznego.
10. Stosowanie profilaktyczne leków przeciwwirusowych nie ma uzasadnienia naukowego.
11. Stosowanie profilaktyki granulopoetynami w czasie stanu zagrożenia epidemicznego powinno dotyczyć chorych z grupy pośredniego ryzyka wystąpienia gorączki neutropenicznej.
12. Każdy chory z podejrzeniem COVID-19 przed przyjęciem w ośrodku onkologicznym powinien mieć wykluczoną infekcję SARS-CoV-2 zgodnie z obowiązującymi rekomendacjami Głównego Inspektoratu Sanitarnego i Ministerstwa Zdrowia.

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Testicular dose contributed by X-ray volume image--(XVI)-guided intensity-modulated radiotherapy (IMRT) in prostate cancer patients

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Introduction: To assess the dose received by testes during XVI-guided IMRT in prostate cancer patients (PCPs).
Material and methods: Testes dose was calculated in 56 PCPs who underwent definitive IMRT using 6 MV or 15 MV photon energies. The dose was measured by thermoluminescent dosimeters (TLDs) MTS-N attached to the scrotum during the first three fractions of IMRT. Testicular concomitant exposure from XVI was measured using a PTW DIADOS E diagnostic dosimeter in ten randomly chosen patients.
Results: The mean and standard deviation values of the average calculated testes dose was 123 ± 117 cGy comprising 1.6% of the prescribed total irradiation dose (Dt). A testicular dose measured by TLDs was 303 ± 110.5 cGy (4% of Dt) and depended on the distance from isocenter to testes (r = –0.8). From one XVI scan, the detected testicular mean dose was 4.3 mGy. Mean XVI scan numbers for all patients was 10.4 so mean concomitant dose in testes was 44.7 mGy (0.06% of Dt).
Conclusions: Testicular dose may be significant in the aspect of fertility during IMRT in PCPs. Kilovoltage XVI-contributed dose to testes seems to be clinically negligible.

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Key words: prostate cancer, testes doses, XVI, IMRT

Introduction

Prostate cancer (PC) is the second most common cancer and the third most common cause of cancer-related death among men in Poland [1]. It is diagnosed mainly in the age group 65–79 years. Prostate-specific antigen (PSA) measurement was introduced to the diagnosis of PC in 1970 resulting in a growing number of younger patients (aged 45–64) suffering from this disease [2]. Radiotherapy (external beam radiotherapy, EBRT or/plus brachytherapy) is a standard treatment modality in localized PC patients (PCPs) [2–4]. As far as EBRT is concerned, it is preferable to use more sophisticated techniques (e.g. intensity-modulated radiation therapy, IMRT) [5, 6]. Epidemiological changes in the PC incidence pattern are enforcing alterations in the approach taken by physicians. It seems that the sexual area and even fertility aspects cannot be neglected in some subset of PCPs. During EBRT delivered to the prostate, the testes, which are in close proximity to this organ, are unshielded. The specific structure (seminiferous tubules are composed of germinal, Sertoli and Leydig cells) and functions of the testes (both reproductive and endocrine) determine their radiobiological response. Germinal cells divide and differentiate to produce spermatocytes, spermatids and eventually spermatozoa or sperm cells. In humans, the transition time from stem cells to spermatozoa is about 74 days. Leydig cells produce the male hormone testosterone.

A mean testicular dose as low as 100 cGy leads to a temporary reduction in the number of spermatozoa while 150 cGy may cause temporary sterility. Azoospermia lasting several years occurs after 2 Gy and permanent azoospermia occurs after a dose of about 6 to 8 Gy in 2-Gy fractions [7, 8]. In turn, even much higher doses have little effect on the Leydig cells in the adult so whereas irradiation of the testes can lead to sterility, it has little or no effect on the libido [7, 9]. What is of paramount importance is the fact that fractionated radiotherapy or even low-doses of scattered radiation reaching the testes during pelvic area irradiation are more harmful to germinal cells than single high-dose exposure. This results from the fact that some proportion of the stem cells move from a radioresistant phase of the cell cycle into more radiosensitive phases in the course of definitive fractionated irradiation [8]. Animal studies have revealed that low-dose radiotherapy would result in persistent double-strand breaks in the spermatogonial stem cells [10], injury to the blood-testis barrier [11] and temporarily observed testosterone abnormal function [12].

IMRT allows the delivery of a higher total dose than 3-D conventional radiotherapy (CRT) to the target volume without exceeding the tolerance dose to the organs at risk (OARs) such as the rectum or the bladder, by careful modulation of photon fluence within a subset of the beams [5, 6, 13, 14]. On the other hand, a considerable increase in the number of beams and monitor units (MUs) for IMRT produces a risk of the delivery of a higher equivalent dose in the OARs located outside the target volume (secondary scattered radiation from the patient) [15]. In addition, tissues outside the primary beam trajectory may be also exposed to low doses of scattered and leakage radiation attributable to imperfections in the radiation delivery devices – secondary scattering from the machine head or the floor and walls of the room [15, 16]. Furthermore, during the course of IMRT, the patient is subjected to an additional dose called "concomitant exposure" from image-guided localization and verification procedures (IGRT), e.g. kilovoltage X-ray volume imaging (kV XVI) [17–20].

Although the dose received by the testes during CRT on the pelvic area guided by portal films has been widely investigated [2, 21–24], little is known about the testes-dose contributed by IMRT (MV energy) and XVI (kV energy) in PCPs. The aim of the present study was to assess the quantity of undesired testicular doses during XVI-guided IMRT for localized PCPs.

Material and methods

The calculations were performed in 56 localized PCPs (Tab. I) who underwent small field step-and-shoot IMRT with curative intent. The work was carried out in accordance with The Code of Ethics of the World Medical Association (the Declaration of Helsinki) for experiments involving humans. Approval for this study was obtained from the Human Care Committee of the Medical University in Bialystok, Poland. Informed written consent was obtained from the patients.

Table I. Characteristics of the studied group – prostate cancer patients (n = 56) treated with definitive small field step-and-shoot intensity-modulated radiation therapy (IMRT)

Characteristics	Value
Age (year), mean min–max	70 54–83
TNM* (n†): T1N0M0 T2N0M0 T3N0M0 T4N0M0	 13 39 2 2
PSA [ng/ml], mean	28.5
Gleason score, mean	6.9
Fraction dose [Gy]	2
Total dose [Gy], mean	74
Total dose [Gy], min–max	66–76
Photon beam energy – X [MV]: 6 15	 29 27

TNM*: T – tumour, N – lymph node, M – metastase; n† – number of patients

Radiotherapy planning and treatment

The IMRTs were planned in accordance with the protocol applied for PCPs in Comprehensive Cancer Center in Bialystok, Poland. Patients were immobilized in the supine position on styrofoam with individually selected accessories such as a knee-fix or feetfix. Next, computed tomography (CT) scans of the pelvic area and testes were performed for patients immobilized in the treatment position, which provided the basis for target and OAR delineation. The clinical target volume (CTV) comprised the prostate and the base of the seminal vesicles (SV). An 8–10 mm margin encompassing the CTV was added to create a planning target volume (PTV). The delineation was comprised of the following OARs: the bladder, the rectum, the heads of the femoral bones and additionally to standard protocol – the testes. Inverse planning Oncentra MasterPlan V 3.3 SP3 (Nucletron, Veenendaal, The Netherlands) with a collapsed cone algorithm (Elekta Corporation, Atlanta, GA) was used to create IMRT plans. Measurements in homogeneous and inhomogeneous phantoms (Alderson Radiation Therapy Phantom, ART) were performed (data not provided) to validate the dose calculation accuracy of the Oncentra Masterplan TPS. In this study, we did not specifically separate the dose from head leakage or collimator scatter which have been measured to comprise 0.5% of the fractionated dose (corresponding therefore to 0.38 Gy for a radiotherapy treatment delivering 76 Gy). IMRT plans were created with a configuration of 7–9 coplanar beams, generated individually for each patient using a 1 cm – multileaf collimater (MLC). All the IMRT plans created by the Oncentra Masterplan TPS were verified using ion chamber arrays including PTW729 and IBA Matrixx systems before treatment. Photon 6 MV or 15 MV beams generated by an

Elekta (Elekta, Stockholm, Sweden) linear accelerator using the XVI technique (Elekta, XVI R4.5) as IGRT were used for the treatment process (Tab. I).

Testicular dose calculated in the treatment planning system (TPS)

Based on the CT datasets of the 56 PCPs, the testes dose was calculated in the TPS. The 3D dose distributions, mean, median, maximum and minimum doses regarding testes were analyzed for a total dose of 76 Gy delivered to the prostate in 38 fractions. The correlation between CTV, PTV volume and testes dose was analyzed.

Testicular dose measured by thermoluminescent dosimeters (TLD)

Thermoluminescent dosimeters (TLDs) MTS-N (Radcard, Krakow, Poland) were attached to the scrotum in close proximity to the testes for each of ten randomly chosen patients during the first three fractions of definitive IMRT (6 MV). Dose measurements were obtained using lithium-fluorine round chips with a diameter of 4.5 mm and a thickness of 0.9 mm. All TLDs were previously prepared in a MagmaTherm laboratory furnace and calibrated. Annealing was started by dosimeters heating to a temperature of 400 ± 5°C for 1 h and this was followed by a cooling down to 80°C for 17 h. Calibration was performed in an X-ray beam of narrow spectrum N-80, N-l00, N-l20, N-150. A Mikrolab RA'04 device (Mikrolab, Krakow, Poland) was used to readout the dose as measured. Final calculations were obtained using calibration factors. The total doses to the testes of each patient were calculated from the mean dose of the three TLD measurements and extrapolated for a treatment course of 38 fractions. The mean distance from isocenter to detector was 12.2 cm. The overall number of TLD measurements was 30. The accuracy of in vivo TLD measurements was verified using an anthropomorphic phantom and multidetector matrix PTW 729 with PMMA phantom.

kV XVI-contributed testes dose measurements

Concomitant testicular dose was measured in 10 randomly chosen patients included in the study. A PTW DIADOS E diagnostic dosimeter with semiconductor detector of the T60004 type (PTW, Freiburg, Germany), previously calibrated in the Central Laboratory for Radiological Protection in Warsaw, was used to measure testes dose contributed by kV XVI. Calibration was performed using an X-ray beam of narrow spectrum N-80, N-l00, N-l20, N-150. The dosimeter was placed in the area of the testes. An M15F1 (M15: medium collimater, size 15 cm; F1: bow-tie filter; 120 kVp, 64 mA, acquisition angle range –180; 180, acquisition time 120s) was used in procedures.

In accordance with protocol, XVI was performed before the 1st, 2nd, 3rd and every 7th fraction as well as in each case of more than 5mm displacement in pelvic area. The number of XVI procedures performed for each patient was counted so that the total testes dose contributed by XVI over the full course of treatment could be calculated.

QA procedures were performed in line with the instructions covered in "Customer Acceptance Tests" as well as "Instructions For Use" in the XVI 4.5 manuals.

The data was statistically analyzed using the computer software Microsoft Excel and Statistica ver.10. Spearman's test ranks were chosen for verification of the hypotheses. A confidence level of 0.05 was accepted. A correlation test of Spearman's ranks was used for correlation analysis, which is a nonparametric measure of statistical dependence between random variables.

Results

MV-testicular dose calculations

The mean and standard deviation (mean ± SD) value of the average testes dose was 123 ± 117 cGy comprising 1.6% of the prescribed treatment dose (76 Gy). The mean values of minimum and maximum doses were 53 and 370 cGy, respectively. The smallest calculated dose in the testes was 0 Gy, the highest – 35.19 Gy (Tab. II).

A trend for increased testes dose in patients irradiated with higher energy was observed. However, dosimetric comparisons between IMRTs using 6 MV and 15 MV photon energies were not significantly different – mean testes doses were 100 *vs* 130 cGy, respectively ($p > 0.05$).

Mean volume of CTV, PTV and testes was 87.5, 264.5 and 57.4 cm^3, respectively. There was no correlation between CTV ($r = 0.2$) or PTV volume ($r = 0.3$) and mean testicular dose.

MV-testicular dose measurements

The secondary testes dose was measured for ten PCPs during the first three fractions of definitive IMRT (total dose 76 Gy,

Table II. Testes doses calculated for prostate cancer patients who underwent definitive small field IMRT (n = 56, prescribed treatment dose 76 Gy, daily dose 2 Gy, SD – standard deviation)

Value	Calculated testes dose			
	Mean dose [cGy]	Median dose [cGy]	Minimum dose [cGy]	Maximum dose [cGy]
Mean ± SD	123 ± 117	122 ± 70	53 ± 42	370 ± 69
Median (25–75%)	98 (56–150)	97 (60–150)	55 (19–78)	102 (160–317)
Min–Max	9–73	9–234	0–166	15–3519

38 fractions, 6 MV photon energy). A mean testicular dose of 7.97 ± 2.9 cGy (min-max 5.17–11.62 cGy) was delivered during one fraction of IMRT (with the mean value taken from 3 measurements for 10 patients). The total testes dose after 38 fractions for these patients was calculated to be 303 ± 110.5 cGy (min–max 196.5–441.6 cGy) and correlated with the distance from the isocenter to the testes (r = –0.84) (Tab. III).

Concomitant kV-testicular dose measurements

In all 10 patients the detector was located outside the XVI verification field. A single XVI procedure delivered a mean dose of 4.3 ± 2.0 mGy (min-max: 2.1–9.1 mGy) to the testes. The mean number of XVI verifications performed during radiotherapy was 10.4 (min-max: 7–16) so that the total mean dose from XVI procedures was 46.3 mGy (min–max: 24.5–136.5 mGy) (Tab. IV).

Conclusions

Testicular dose contributed by megavoltage IMRT, as well as concomitant dose added by the kV XVI procedure were analyzed in the current study. According to the data indicated in the literature, the testes dose originating from neutrons generated at high energies is very small (0.04% of the treatment dose) and has not been taken into consideration in this analysis [25, 26]. Unfortunately, the minimum dose which affects testes function in irradiated PCPs has not been precisely determined. Based on patient studies of testicular injury following conventionally fractionated irradiation, it seems that doses smaller than 20–50 cGy should not cause hormonal impairment [22, 24] while doses ranged 100–350 cGy are sufficient to impair germinal cells [7, 24, 27–32]. The standard total dose applied for PCPs treated with definitive IMRT in the present study was 76 Gy (38 fractions). The dose constraints were not specified for the testes to determine the dose distribution in a standard situation where testes are not contoured as critical structures. We found that for these patients the mean doses to the testes were 123 cGy (calculated by TPS) or 303 cGy (measured by TLDs), comprising 1.6 or 4.0% of the total treatment dose. The difference between the calculated and measured doses may result from the fact that TLDs detected only a superficial dose in one point of the scrotum while TPS assessed the dose distribution throughout the whole organs. Moreover, it is well known that TPS may undercalculate the peripheral dose in irradiated patients [33].

Table IV. Assumed XVI-contributed testes dose for whole course of treatment (10.4 scans)

Testes dose per scan [mGy]		Testes dose (10.4 scans) [mGy]	
Mean ± SD	Min–Max	Mean	Min–Max
4.3 ± 1.99	2.1–9.1	44.7	21.84–94.64

Importantly, the doses detected by both methods indicate that IMRT may be associated with testes function impairment if no constraints are determined during the planning process. If the testes are not imaged and delineated, the treatment planning system does not regard them as "worth-protection", resulting in beam fluence through the genitalia. Additionally, a high number of MUs delivered during IMRT may increase internal scattering leading ultimately to a clinically significant testicular dose. Intensity modulation techniques require the accelerator to be energized 3–4 times longer than that for 3D-CRT methods, thus increasing linear accelerator head leakage and the overall exposure of the patient to secondary radiation [15, 23, 34–37]. The equivalent doses for the whole body produced by IMRT are greater than those seen when using conventional radiation [38, 39]. On the other hand, due to multileaf collimater (MLC) movements, the effective field size in IMRT is smaller than in 3-D CRT which may help reduce the dose received by nearby out-of-field organs, such as the gonads in PCPs [15, 34, 39]. The results of other studies have shown that the testes, despite the increased number of MUs for IMRT, receive as much as a 2.5 times lower dose during IMRT than 3-D CRT when regarded as critical structures [34, 40]. Data presented by Deng et al. [41] and Martin et al. [42] showed that, during definitive IMRT, testes doses contributed by photon scattering may be as low as 0.7–1.4 cGy per fraction (in our study – 3.2 cGy). Basing on the available literature, mean testicular doses from CRT calculated to 76 Gy ranged from 206.9 to 234 cGy comprising 2.72–3.08% of the prescribed dose, thus being higher than the doses presented for IMRT [2, 21, 31]. This is why dynamic techniques are the method of choice in PCPs with plans for a family, providing the testes are given high priority as an avoidance structure in order to minimize beam fluence through the genitalia.

In addition, our findings suggest that lower MV-energy is associated with reduced testicular dose. These results are

Table III. Testes dose measured for prostate cancer patients who underwent definitive 6 MV small field IMRT (n = 10, prescribed treatment dose 76 Gy, daily dose 2 Gy)

Value	Measured testes dose		Distance isocenter-detector [cm]
	One fraction – 2 Gy [cGy]	38 fractions – 76 Gy [cGy]	
Mean ± SD	7.97 ± 2.9	303 ± 110.5	12.2 ± 1.35
Median (range 25–75%)	6.74 (5.8–10.5)	256.1 (220.8–399.8)	12 (11.6–13.5)
Min–Max	5.17–11.62	196.5–441.6	9–14.5

in agreement with other studies which have shown a weak dependence of photon dose outside the treatment field on beam energy [16, 43]. According to King et al. [44] the photon scattered dose in the testes is about 1.3 times higher with 15 MV beams compared with 6 MV beams. The dependence of testicular dose on CTV/PTV volume was also described [44–46]. In our study, where all patients were irradiated on small fields, a correlation between CTV, PTV volume and mean testicular dose was not observed.

It would be impossible to determine on the basis of this study what the exact components of the measured dose are. According to van der Giessen [43], the major contributors of dose to tissues in close proximity to the field edge are collimator scatter and patient scatter. As the distance increases from the field edge collimator scatter decreases, and patient scatter, as well as head leakage, becomes more dominant [15, 47, 48].

In the current study, the testicular dose decreased with increasing distance from the isocenter to the testes. Many studies have shown such an association and out-of-field dose data are often presented as a function of distance from the field edge or central axis relative to the tumor target in the patient [15, 19, 47, 49, 50].

Concomitant exposure – XVI

It is assumed that the additional imaging dose should be lower than 2% of the therapy dose variation in order to comply with the ALARA convention rule [51]. In the present study we found that kV XVI increased the total testicular dose by 4.3 mGy per fraction (max 9.1 mGy). There are very few studies in the literature exploring the impact of CBCT-based prcoedures (XVI Elekta, Varian OBI system) on the testes dose in PCPs [35, 50]. Both Hyer et al. [52] and Deng et al. [41] determined the mean testicular dose from one procedure of CBCT as 29 mGy. Most importantly, the results from the Deng study comprise mean testes doses for different OBI field spans. The testes dose for a 30 cm-field produced 57 mGy while for 10 cm-field – only 2 mGy (this calculation is similar to ours, received for a 15 cm XVI field from the measured method). In Hyer's investigation [52], the detector was placed in some cases within the XVI field which also increased the testes doses and may explain the differences with the present study where the detector was never located in the field. The testes concomitant dose deserves additional investigation on a large group of patients with different XVI settings.

The results of the current study indicate that the dose in the testes may be significant from a fertility perspective during IMRT in PCPs. It seems that the IMRT protocol for PCPs who have not completed family planning should involve the determination of the testes as an avoidance structure to keep the dose as low as reasonably achievable during the optimization process. The kilovoltage XVI-contributed dose to the testes seems to be clinically negligible, especially if verifications are performed once or twice a week using a small field span. To minimize the testicular dose in PCPs with plans for a family, the establishment of a specific quality assurance protocol for XVI-guided IMRT is warranted.

Conflict of interest: none declared

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Oncogeriatrics (part 5.)
The role of comorbidities in older patients with cancer

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Comorbidity is defined as the presence of one or more additional conditions co-occurring with primary indices. Comorbidity is common in older cancer patients. Its prevalence, however, is difficult to determine and varies by cancer site. There is no single reason for which comorbidity and cancer coexist, but chronic diseases and cancer are both common in older age and share many risk factors.

There is no consensus on how should comorbidity be measured. Even though many comorbidity indices have been developed so far, no unified, widely used instrument exists.

Patients with comorbidities have worse outcomes compared to those with no such conditions. They may experience diagnostic and therapeutic delay and be disqualified from radical treatment more often. Moreover, they are more likely to suffer from treatment-related complications and have worse overall survival.

It seems important to assess the comorbidity status as a part of individualised oncologic treatment planning. However, as data regarding its significance are insufficient and in many cases conflicting, patients with comorbidity should not be routinely considered as not fit enough for a radical treatment. Therefore, to adequately address all of the concerns that have been raised, a broader participation of older, comorbid patients in clinical trials is needed.

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Key words: older patient, comorbidity, multimorbidity, frailty

Introduction

Almost all chronic diseases are more prevalent in elderly than younger individuals, and so is cancer. That is why taking care of oncology patients who suffer from multiple, concurrent comorbidities is an everyday job [1]. Nevertheless, such patients are still often excluded from randomised controlled trials, making it difficult to generalise results and establish relevant clinical guidelines [2]. This, in turn, leads to diagnostic and treatment dilemmas. Older patients with comorbidity are often disqualified from radical therapy, receive suboptimal care, and suffer from various adverse events: prolonged hospitalisation, institutionalisation, decreased quality of life, and higher complication rates and mortality [3]. Despite the fact, that comorbidity is considered important by most clinicians, there is no consensus on definition, way to measure it, and its role in geriatric assessment. It also often gets confused with other terms, which are related to but not synonymous with comorbidity, such as multimorbidity, polypharmacy, frailty or disability [1].

Definition and etiology

The problem of comorbidity was firstly addressed in 1970 by Feinstein, who noticed its influence on the diagnostic and therapeutic process and defined it as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient that has the index disease under study" [4]. Since that time, the term has been used in multiple studies indicating either a disease coexisting with the primary disorder simultaneously, but independently, or every additional condition, even one related to the "index" disease. The concept

of comorbidity is important not only in clinical medicine, but also in public health and epidemiology, which explains the need for different definitions and approaches to its measurement [5]. For the clinicians' purposes, it seems most appropriate to acknowledge that **comorbidity is the presence of one or more additional conditions co-occurring with a primary condition**. Regarding oncological patients, in most cases cancer is considered the primary, index disease, while other disorders are named as comorbidities.

Considering the etiology of comorbidity, Valderas et. al. [5] suggested five main pathways in which the co-existing diseases may be associated:

1. There is no etiological association between the diseases (two diseases occur by chance e.g. lung cancer and psoriasis)
2. One of the diseases is a direct cause of the other (e.g. brain tumor and epilepsy)
3. The risk factors for each disease are correlated (e.g. risk factor1: smoking → disease1: chronic pulmonary obstructive disease; risk factor2: alcohol→ disease2: Hepatocellular carcinoma)
4. The risk factors for each disease are not correlated, but each can cause either disease (e.g. risk factor 1: smoking; risk factor 2: age, disease 1: ischaemic heart disease; disease 2: lung cancer)
5. The symptoms of each disease are in fact all caused by another, undiagnosed disease (e.g. disease1: tension headaches, disease2: hypertension, disease 3: pheochromocytoma) [5].

In older patients, however, such interrelations are difficult to follow, as their comorbidities are often multiple, long-lasting and co-exist with functional decline. Nevertheless, looking for possible causes and associations between particular conditions is essential, as in some cases the onset of comorbidity can be predicted, or a single intervention may address more than one health issue. It is also worth mentioning that oncological treatment itself may cause or worsen comorbidity. While cancer often becomes a chronic condition, this mechanism seems to be of growing importance [1].

How can we measure comorbidity?

There is no "gold standard" regarding comorbidity measurement, as none of the existing approaches is optimal for all purposes. The simplest way is to divide patients into two groups: with or without comorbidity; or to simply count the prevalence of all comorbid conditions. However, defining what a comorbid condition is may be difficult, resulting in weak repeatability and the poor prognostic value of this approach. The problem may be solved by the use of comorbidity indices. The most popular ways to quantify the problem of comorbidity are simple condition counts, organ-based systems or weighted indices (Tab. I).

While choosing the measure of comorbidity, the key considerations are [16]:

1. **What is the cancer site?** As some of the measures have been developed specifically for a particular disease, it seems appropriate to use them if applicable.
2. **What is the endpoint to predict?** The indices have been developed to predict different outcome measures e.g. 10-year mortality, cancer survival, postoperative mortality etc. It would be reasonable to use the index with the highest possible validity for the particular clinical or research question.
3. **What kind of data and how much time do we have?** Some of the indices require a lot of specific information that is unavailable or assessment may be too time-consuming. The choice should be, though, adjusted to the clinical situation or research plan.

Unfortunately, there is still a great inconsistency in approach to the analysis of comorbidity status. The prognostic value, validity, reliability and feasibility of different measures is often questioned, making clinicians unclear about their usefulness and generally unwilling to use them on a regular basis [16].

Epidemiology

The burden of comorbidity in older cancer patients is of increasing concern. Its prevalence is generally high, but differs depending on the population included and research methodology (e.g. type of cancer, age range, way in which comorbidity was assessed). Regarding lung cancer, in patients aged ≥70 several authors reported that 80–83% of patients had CCI ≥1 [17–19]. In oesophageal cancer patients aged ≥65, prevalence of comorbidity (CCI ≥1) was also high and ranged from 70–80% depending on the study [20–22]. Among individuals aged 65 or more suffering from head and neck cancer, Dziemiańczyk-Pakieła et. al. reported comorbidity in 62% of patients, based on a list of diagnoses available in medical records [23]. In older patients with colon cancer (≥65 y), however, comorbidity (CCI ≥1) was present less often as its' prevalence ranged from 32–52% [24–26]. In a US study of 49 616 women with breast cancer, 23% of patients aged 85–89 and 11% of patients aged 67–69 had severe comorbidity (CCI ≥2) [27]. In general, studies with more inclusive measures of comorbidity show a higher percentage of affected patients. It also seems to be more common in those with certain cancer types, especially smoking-related cancers such as lung, head and neck or bladder cancer [28], and in reports based on questionnaires or review of medical notes, rather than in those based on administrative data [29–31]. Analysis of the prevalence of different types of comorbidity is difficult, as most authors uses indexes, rather than list all of the the diagnoses. Most likely, however, the spectrum of diseases coexisting with cancer reflects the distribution of disorders in the general populations of the elderly. For example, in a Dutch registry of patients with breast, lung, colorectal, prostate and ovarian cancer aged ≥70, most common were heart disease, cerebrovascular and peripheral vascular disease, hypertension, pulmonary disease and diabe-

Table I. A summary of the characteristics of frequently used comorbidity indices

Index name	Author, year	Clinical purpose	Items included	Severity of assessed items	Scoring	Score range
ASA	Saklad et al., 1941 Last Amended: ASA House of Delegates, 2019 [6]	to assess and communicate a patient's pre-anesthesia comorbidities. The classification system alone does not predict the perioperative risks	overall physical status	does not apply	does not apply	1–6
CIRS	Linn et al., 1968 [7]	physical impairment assessment for various clinical uses	13/14 systems	0–4	summative	0–56
KFI	Kaplan and Feinstein, 1974 [8]	to predict 5-year mortality due to the comorbid conditions in patient with type II diabetes	12 systems	1–3	highest score	1–3
CCI	Charlson et al., 1987 [9]	to predict risk of death from comorbid disease during 10-years follow-up	17 conditions	1–6	summative	0–33
ICED	Greenfield et al., 1993 [10]	to predict the impact of comorbidity and functional status on the 1-year postoperative complications and quality of life after total hip replacement	14 systems +10 functional impairments	0–4 (comorbidity) 0–2 (functional status)	highest scores of both dimensions	0–3
Satariano Index	Satariano et al., 1994 [11]	to predict the effect of comorbidity on 3-years survival in breast cancer patients	7 conditions	unweighted	condition count	0–7
Elixhauser Comorbidity Index	Elixhauser et al., 1998 [12]	assessment of comorbidity using administrative data	30 conditions	conditions analysed separately	does not apply	does not apply
Elixhauser Point System	van Walraven et al., 2009 [13]	to derive an index from Elixhauser conditions	21 conditions	β-coefficient	summ of β-coefficients	–19 to 89
ACE-27	Picirillo et al., 1996 [14]	assessment of comorbidity in oncological patients	27 conditions	1–3	highest score of single item	1–3
CPS	Evans et al., 2012 [15]	assessment of the severity of comorbid conditions in trauma patients	all known conditions + all pre-injury medications	unweighted	summative	0–n

ASA – American Society of Anesthesiologists Physical Status Classification System; CIRS – Cumulative Illness Rating Scale; KFI – Kaplan-Feinstein Index; CCI – Charlson Comorbidity Score; ICED – Index of Coexistent Disease; ACE-27 – Adult Comorbidity Evaluation-27; CPS – Comorbidity-Polypharmacy Score

tes [32]. In recent years, researchers have also tried to examine so-called patterns of comorbidity, as certain diseases seem to occur in typical clusters (e.g. cardiopulmonary, cardiovascular, metabolic, neurological/mental health etc.). This approach may facilitate development of prevention strategies and clinical practice guidelines, but considering older cancer patients, the existing data is still insufficient [33, 34].

How does comorbidity affect cancer outcomes?

Cancer outcomes may be influenced by comorbidity on many levels, starting from screening and detection, through choice of treatment, adherence and compliance, ending with treatment response and complications.

The presence of comorbid conditions may blur the classical clinical presentation of cancer, resulting in diagnostic delay. It is no surprise that diseases like dementia, alcohol dependence or other psychiatric disorders have been associated with late cancer diagnoses [33]. Also, the greater number of comorbid conditions has been shown to be associated with **longer cancer diagnostic intervals** [35]. As physicians are usually focused mostly on the chief complaint, comorbid patients may **receive screening procedures less often**. For example, that is why in a Canadian cross-sectional study, patients with depression were found to receive colorectal cancer screening recommendations less often [36]. With fewer resources and social support, older patients with chronic diseases may also **experience difficulties with travelling to medical facilities**. Moreover, such individuals (especially the oldest) may be simply less interested in undergoing life prolonging procedures [37]. On the other hand, comorbid patients are more likely to use medical services. They may undergo preventive follow-ups more often and so benefit from oncological alertness. This positive impact, however, seems only to occur in certain comorbidity types. Fleming et al. reported that women who had cardiovascular, musculoskeletal, gastrointestinal, genitourinary disease, or osteoarthritis had 7%–24% lower risk of developing

advanced breast cancer. Conversely, however, they found those with diabetes, renal, endocrine, psychiatric, haematological disease, osteoporosis, obesity and AIDS to be at 11%–20% higher risk of being diagnosed with cancer at an advanced stage [38]. Other studies analysing the use of mammography, PSA, Pap smear and colorectal cancer screening between patients with different comorbidity burdens have also had mixed results, reporting either higher or lower risk of being diagnosed with an advanced disease [39]. While cancer screening is in many ways related to comorbidity status, a common dilemma is whether a chronically ill patient may benefit from early cancer detection. Unfortunately, as no recommendations are available in this matter, they probably often get either under- or over-screened [39]. The presence of comorbidity has also been associated with **prolonged time from diagnosis to treatment**, as a certain amount of time is needed to consult the patients with other specialists or to stabilise their chronic diseases [40].

A general belief that **patients with comorbidities have poorer overall survival compared to those without comorbidities** has been confirmed by most researchers. The systematic review of observational studies, which analysed the impact of comorbidity on breast, colorectal and lung cancer outcomes, showed that in breast cancer patients the 5–7 years mortality was 1.1 to 5.8-fold higher in patients with comorbidity, among patients with colorectal cancer the 5-year mortality was 1.2 to 4.8-fold higher, and in lung cancer (1–5 years follow-up) 1.1 to 1.5-fold higher. The lowest difference in survival time in lung cancer patients was most likely due to the fact that the effect of comorbidity on the overall mortality seems to be more evident in highly curable cancers. Patnaik et al., for example, who analysed a cohort of 64 0034 women with stage I breast cancer (known for its favourable prognosis), found that in patients with serious comorbidities, the outcomes have not corresponded with survival rates of early--stage cancer, but were comparable to later-stage tumours [27]. Even though comorbidity has generally been associated with so-called "death due to causes other than cancer", several authors reported increased cancer-specific mortality in comorbid patients as well [41–43]. The question is, though, whether comorbidities may **influence the histological features of cancer**. It seems possible that chronic inflammatory state, hyperinsulinemia or immunosuppression are associated with more aggressive cancer growth and higher grade [43–45]. On the other hand, commonly prescribed drugs, such as non--steroid anti-inflammatory agents or statins, are considered to be protective against cancer [46–48].

Another concern while dealing with older, comorbid patients is the choice of treatment. According to a recent systematic review, some of the older cancer patients themselves considered comorbidity as an important reason for declining cancer treatment [49]. As far as the physicians' decisions are concerned, a common pattern, observed by most researchers, is a **higher rate of disqualifications from surgery in comorbid patients** [50, 51]. The question is, however, whether older patients with comorbidity are in fact at a higher risk of developing postoperative complications, and if so, which comorbidities are important. Unfortunately, regarding older cancer patients, data about its impact on surgical treatment effects are scarce. Most of the authors present data for patients of all ages. Yvette et al., who analysed 8583 gastrointestinal cancer patients from the Netherlands, found several comorbidities derived from CCI (cardiac disease, vascular disease and previous malignancy in colon cancer; vascular disease in rectal cancer) to be independent risk factors for 30-day mortality according to multivariate logistic regression analysis [52]. In another large study from the Netherlands (4911 colon, 2674 rectal, 2385 NSCLC and 8501 breast cancer patients), Janssen-Heijnen found that several complications occurred more often in patients with certain comorbidities, but none of them turned out to be significant in the multivariate logistic regression analysis [53]. Analysing the results of 214 patients undergoing gastrectomy, Hamakawa et.al. showed that only pulmonary (OR = 2.69) and vascular disease (OR = 5.46) were significantly associated with postoperative complications in the multivariate analysis [54]. Wang et al. reported that among 1,657 patients undergoing laparoscopy-assisted total gastrectomy the presence of comorbidity (≥1 coexisting disease) was a risk factor for local (OR = 1.20) and systemic complications (OR = 1.24). They also found specific diseases such as diabetes mellitus, anaemia, and pulmonary and renal disease to be the risk factors for abdominal bleeding, anastomotic leakage and pneumonia [53]. Nevertheless, generalising such results for the population of elderly people may be misleading. Kim et al., who have analysed the results of patients after laparoscopy-assisted distal gastrectomy found that in all the patients included, comorbidity was a predictive factor for systemic complications in the multivariate analysis. However, after dividing the patients into two subgroups (1: <60 y, 2: ≥60 y), comorbidity remained a significant risk factor (OR = 3.32) only in patients aged ≥60 [55]. In a study based on Surveillance, Epidemiology, and End Results–Medicare Registry, which included 149,622 patients aged 75 or more, CCI ≥3 was found to be a risk factor for 30-day readmission after colorectal cancer surgery (OR = 1.27) [56]. Regarding the Polish population, the authors of this review performed a logistic regression analysis among 600 individuals aged ≥65 undergoing elective high risk abdominal surgeries (60% of cancer patients) and found psychiatric (OR = 4.4) and kidney disease (OR = 2.74) to be the independent risk factors for 30-day mortality, and heart disease (OR = 1.67) to be the independent risk factor for 30-day major complications (unpublished data). For now, however, the variation in study outcomes makes it difficult to draw certain conclusions, which may be useful in clinical practice.

Moreover, comorbid patients are also **less likely to receive adjuvant therapy and to complete chemotherapy treatment**. According to existing data, comorbidity may predispose

to **development of chemotherapy-related toxicity**, so they often receive a reduced chemotherapy dose [57–60]. To assess the pharmacological treatment safety, however, data from clinical trials would be most relevant. Even though the American Society of Clinical Oncology (ASCO), Friends of Cancer Research, and the US Food and Drug Administration recently recommended changing the criteria used to exclude comorbid patients from cancer clinical trials, the presence of comorbidities is still adversely associated with trial discussions, offers and participation [61].

Conclusions

Comorbidity is common in older cancer patients. Its prevalence, however, is difficult to determine and varies by cancer site. There is no single reason for which comorbidity and cancer coexist, but chronic diseases and cancer are both common in older age and share many risk factors. Also, the treatment of one condition may be involved in the development or affect the course of another disease.

There is no consensus on how comorbidity should be measured. Even though many comorbidity indices have been developed so far, no unified, widely used instrument exists.

Patients with comorbidities have worse outcomes compared to those with no such conditions. They may experience diagnostic and therapeutic delay and be disqualified from radical treatment more often. Furthermore, they are more likely to suffer from treatment-related complications and have worse overall survival.

It seems important to assess comorbidity status as a part of individualised oncological treatment planning. However, as data regarding its significance are insufficient and in many cases conflicting, patients with comorbidity should not be routinely considered as not fit enough for radical treatment. Therefore, to adequately address all of the concerns that have been raised, broader participation of older, comorbid patients in clinical trials is needed.

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Contouring of the left anterior descending coronary artery in patients with breast cancer – the radiation oncologist's view

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Breast cancer is the cancer with the largest prevalence, both in Poland and worldwide. The standard treatment in patients with this disease is breast-conserving therapy (BCT), followed by whole breast radiotherapy (WBRT) with a boost dose applied to the area of the bed created after tumour resection. In women who have undergone breast amputation – in the presence of poor prognostic factors – the chest wall is irradiated with or without the irradiation of the axillary fossa and clavicular area. Radiotherapy is used as an adjuvant treatment in connection with the high rate of relapses in the area of the treated breast – as much as 20% after 10 years. Some patients, before the commencement of the irradiation, are treated systemically with the use of regimens comprising drugs with a high degree of cardiotoxicity. This effect may even be increased during the course of radiotherapy – mainly in patients after amputation of the left breast. The side-effects induced by radiotherapy depend on area of the heart within the field of irradiation. Studies suggest that the vulnerable parts of the heart are the coronary vessels, and primarily, the left anterior descending (LAD) artery, which is located close to the chest wall.

The objective of this study is to present practical guidelines concerning contouring the left anterior descending (LAD) artery in patients with cancer of the left breast, who have qualified for radiotherapy.

Contouring the LAD seems to be significant as a method of assessing the critical organ during radiotherapy. The results may cause a modification of the treatment strategy: a change to the planned radiotherapy, the quantity of the beams and/or their angle of incidence or a change in the beam weight.

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Key words: LAD, radiotherapy, breast cancer

Introduction

Breast cancer is the most frequently occurring type of cancer, both in Poland and worldwide [1]. The standard treatment in patients with this disease is the breast-conserving therapy (BCT), followed by whole breast radiotherapy (WBRT) with a boost dose applied to the area of the bed created after tumour resection. In women who have undergone breast amputation – in the presence of poor prognostic factors – the chest wall is irradiated with or without the irradiation of the axillary fossa and clavicular area. Radiotherapy is used as an adjuvant treatment in connection with the high rate of relapse in the area of the treated breast – as much as 20 % after 10 years [1, 2].

Some patients, before the commencement of the irradiation, are treated systemically with the use of the regimens comprising drugs with a high degree of cardiotoxicity. This effect may even be increased during the course of radiotherapy – mainly in patients after amputation of the left breast.

The objective of the study

The objective of the study is to present practical guidelines concerning contouring the left anterior descending (LAD) artery in patients with the cancer of the left breast, who have qualified for radiotherapy.

Materials and methods

50 patients treated in the Radiotherapy Department of the Oncology Centre in Bydgoszcz were qualified to the study. All the patients had breast cancer and had been surgically treated: in 14 of them a breast had been amputated, and in 36 of them BCT (breast conserving therapy) had been applied. All the women had indications for adjuvant radiotherapy. After qualification for the treatment, a routine CT for radiotherapy planning was performed (Tab. Ia, Ib, Ic).

CT was performed in patients in the lying position with limbs abducted and rotated with the use of a Posirest support. Before assessment, a tracer was applied on the entire length of the scar. The scans were made every 3 mm, during free and gentle breathing, whilst the images were sent to an Eclipse planning system with the use of a DICOM system. In each patient apart from the standard clinical target volume (CTV) and risk organs, LAD was contoured. One examiner identified the location of the LAD on the basis of the course of the anterior interventricular sulcus, whilst the other (in an independent manner) – controlled the LAD contouring.

In the patients who had undergone breast amputation, the area of clinical target volume (CTV) comprised the entire chest wall together with the resection bed, skin, muscles, deep fascia and ribs; with a margin of 0.5 cm to the planned target volume (PTV) and adaptation to the anatomic structures with a total dose of 45 Gy in 20 fractions. In the patients who had undergone BCT, the CTV area comprised the entire breast and the tumour resection bed, sparing the lower lying muscles, ribs and skin; with a margin of 0.5 cm to PTV and adaptation to the anatomic structures with a total dose of 42.5 Gy in 17 fractions. In some patients a boost was carried out with brachytherapy, at a dose of 10 Gy in 1 fraction, whist in the remaining patients – with the use of and external beam at a total dose of 10–12 Gy in 4–6 fractions, with 2–2.5 Gy per fraction.

In radiotherapy planning, most frequently, 2 tangential fields with adaptation of the posterior border were applied, with the use of mechanical and/or dynamic wedges of 15–30 degrees and photon radiation with the energy of 6 and 15 MeV. In the majority of patients who had undergone mastectomy, a tissue-like bolus was required, whilst some patients who had undergone BCT needed a strip of tissue-like bolus in the midline.

Results

After analysis of the contouring of LAD in 50 patients by 2 independent examiners and after comparison of their drawings, the following conclusions were drawn:

1. The LAD is invisible in some places and its location should be interpolated from the previous scans.
2. The LAD is best visible in women with coronary atherosclerosis.
3. Coronary vessels are best visible for contouring in the windows from +600 to 800 and –150 to –200 Hausfield units (HU).
4. The easiest way to identify the LAD is to begin with the upper part of the heart, where this artery is located between the left and right heart ventricle and to right of the descending aorta – i.e. in the place where the LAD

Table Ia. Mean maximum dose (Dmax), mean minimum dose (Dmin), mean average dose (Dmean) and mean median dose (Dmed) for the heart and LAD in all patients

	Dmax (Gy)	Dmin (Gy)	Dmean (Gy)	Dmed (Gy)
Heart	42.10	0.57	5.08	1. 87
LAD	41.46	3.21	30.03	32.22

Table Ib. Mean maximum dose (Dmax), mean minimum dose (Dmin), mean average dose (Dmean) and mean median dose (Dmed) for the heart and LAD for the patients who had undergone BCT

	Dmax (Gy)	Dmin (Gy)	Dmean (Gy)	Dmed (Gy)
Heart	42.62	0.58	5.96	2.34
LAD	40.94	3.91	32.11	35.45

Table Ic. Mean maximum dose (Dmax), mean minimum dose (Dmin), mean average dose (Dmean) and mean median dose (Dmed) for the heart and LAD for the patients who had undergone mastectomy

	Dmax (Gy)	Dmin (Gy)	Dmean (Gy)	Dmed (Gy)
Heart	41.39	0.42	5.45	1.48
LAD	41.31	3.46	31.05	32.63

branches away from the main left coronary artery, and then runs towards the front and down towards the heart apex.

5. There were significant differences observed between specific CT scans with regards to the location of the LAD, which were connected to its tortuous course, and which led to significant difficulties in interpolating its location on the next scans.
6. The vessel is so small near the heart apex that it is rarely visible.
7. In about 1/3 of the upper part of the heart LAD is poorly visible; the anterior interventricular sulcus must be located as the artery runs in this area.
8. During contouring, it was observed that the LAD in 1/2 or 1/3 of the heart length is adjacent to the chest wall from the inside (this concerned the majority of the patients).
9. The area in which the LAD was adjacent to the chest wall was largest in women with heart disease and the vessel did not have a circular cross-section,
10. In the group of young and very slim patients, there were cases in which the LAD and the entire heart were not adjacent to the chest wall so the dose applied to these structures was minimal and, moreover, the cross-section of vessel in these patients was circular, which significantly facilitated its identification.
11. In patients with a lower body mass index, a thinner chest wall and/or a small amount of fatty tissue in the pericardium, the dose per LAD was higher than in patients with a larger amount of the pericardial fatty tissue, which isolated the LAD from the chest wall, thus increasing the distance between them.
12. A comparison of the contouring of the left anterior descending (LAD) artery made by two independent examiners did not reveal any significant differences, and these differences decreased even more with an increase in the experience in locating the vessel and in precision in contouring,
13. When, in accordance with the suggestions of other authors, a 1 cm margin was added around the vessel with regard to difficulties in contouring and the respiratory mobility of the heart, all the patients then had the LAD located in this area, irrespective of the person who performed the contouring of the risk organ; and when the examiners had more experience in contouring, a margin of 0.5 cm was sufficient.

Discussion

Clinical studies carried out among patients with breast cancer point to the benefits in adjuvant radiotherapy, after both BCT and breast amputation, where the risk of recurrence is high. The side-effect connected with radiotherapy is an increase in cardiological incidents, which might lead to death [3–5].

Irradiation may cause 2 types of cardiovascular disease: micro- and macrovascular diseases. The first group is characterised with a decrease in the density of the vessels within the heart leading to chronic heart ischemic disease and myocardial infraction secondary to focal degeneration. In macrovascular diseases, in turn, irradiation accelerates and/or intensifies the development of coronary atherosclerosis [6].

Currently, many strategies are applied in order to minimize the effects of systemic treatment and/or radiotherapy. Modern methods of reducing cardiotoxicity comprise radiotherapy planning techniques: the use of coplanar beams, megavolt energy, intensity-modulated radiotherapy (IMRT), deep inspiration breath hold (DIBH), spiral tomotherapy or irradiation with the use of special immobilisation used when a patient is in the prone position – for women after breast conserving surgery [2, 6].

Retrospective studies carried out among women with breast cancer showed a significant effect of irradiation on the heart and, consequently, an increase in the cardiotoxicity of this type of treatment; some correlation was observed between the mortality rate and the dose-volume histogram (DVH) in this critical organ, namely the heart [3–5].

Radiotherapy-induced adverse effects depend on the region of the heart which is contained in the field of irradiation. Studies suggest that these important areas are made up of the coronary vessels, and, primarily the LAD, which is located in close proximity to the chest wall. The LAD contouring seems, therefore, significant for the assessment of the critical organ during radiotherapy. The results of contouring may influence the modification of the treatment strategy: a change of the technique of the planned radiotherapy, the quantity of the beams and/or their angle of incidence or a change of the beam weight [7, 8].

The results of many clinical studies suggest that patients with cancer of the left breast are exposed to a larger risk of cardiovascular complications than those with cancer located in the right breast [2, 4, 5]. Tanaka states that in patients with breast cancer receiving radiotherapy, the mortality rate connected with heart disease was between 1.27 and 1.76 times higher than in patients without radiotherapy [9]. Borger et al. estimated that for patients with left breast cancer who received radiotherapy with the use of tangential fields, the rate of cardiological complications was 1.38 (95% confidence interval: 1.09–2.15) in comparison with a location in the right breast [10].

It must also be remembered that patients with breast cancer make up a group in whom radiotherapy planning is very difficult – in particular in women after mastectomy, in whom the chest wall thickness is very low, which increases the quantity of the irradiation deposited in soft tissue. This leads to the fact that a larger dose is administered to the lung and/or heart parenchyma, and that dose is also administered onto a larger area [2]. Studies clearly show that each dose increase by 1 Gy for the heart, results in an increase of mortality rate by 3% within 20 years [2]. In patients with chest wall radiotherapy, asymptomatic disorders of the perfusion of the heart

vessels, occurring within 6 to 24 months of the completion of radiotherapy are observed [11, 12]. There are some individual reports which exclude the effect of radiation dose on the heart, yet these reports were published in the last century, where treatment planning and realisation were completely different so now it is difficult to make any reference to these reports [2].

The largest difficulty in contouring the LAD is the fact that in the majority of centres no contrast agent is administered for the CT when planning radiotherapy. This significantly deteriorates the visibility of the course of the vessel, in particular given the fact that this artery is very small and has a tortuous course, and its diameter is usually 3 mm (and at the apex – about 1 mm) [13].

Venarini et al. used computed tomography with optimum image resolution obtained thanks to a detector measuring 0.5 mm, yet the patients' breath and the kinetics of circulation led to blurring of the image, which made imaging of the LAD very difficult [13]. During the contouring process it was observed that the left anterior descending artery, in 1/2 or 1/3 of its length, is most frequently adjacent to the chest wall from inside. In this very place, the LAD is also located close to the sternum, and, because of this location and the necessity of irradiating the whole chest wall in patients who have undergone breast amputation, when adding a margin to clinical target volume (CTV), the LAD lies within the planned target volume (PTV). This allowed the clinicians to draw conclusions and introduce corrections while contouring and treatment planning. Much more attention was paid to the correctness of the LAD contouring and target volumes so that the part of the artery within the field of the therapeutic beam could be limited and/or the creation of "hot spots" i.e. areas of high dose could be reduced.

Venarini et al. assessed the location of the left anterior descending artery in 25 breast cancer patients and presented practical guidelines for contouring this structure. They emphasised that the location of the LAD is, in some places, invisible, and therefore must be interpolated from previous scans, whereas the visibility of the vessel is also negatively affected by artefacts created by breathing and the heartbeat [13].

Jagsi et al. [14] in turn, evaluated the size of the relocation of the left anterior descending artery in a group of 10 patients and observed that the largest movements of the LAD occur in the vertical (up and down) plane. At the same time, they stressed that a good visualisation and the possibility of contouring allowed for the exclusion of the LAD from the irradiated volume. Venarini et al. in their study, specified the doses for critical organs, and found that the observance of these doses may have some influence on the protection of those organs. They calculated the maximum admissible dose for the LAD, being for D2% from 2.7 to 41.7 Gy, and V 25 Gy for the heart should be lower than 6%, and most frequently it was 1.5% with standard deviation being +/–2.1% [13].

Di Franco et al. [6] pointed to difficulties in LAD contouring, observing, at the same time, that with regards to the difficulties in contouring and the respiratory mobility of the heart, a 1 cm margin should be added around the vessel [6]. In our opinion, a 0.5 cm margin is sufficient around the LAD, provided that the examiner has gained practical skills in contouring. Certainly, in patients with large respiratory mobility of the heart and with difficulties in vessel visualisation, adding a 1 cm margin might turn out to be necessary.

In the case of patients with a burden of cardiological comorbidities, a selection of other radiotherapy planning and realisation techniques must be taken into consideration. The DIBH technique is one of the ways of minimising the dose of radiation for the heart and coronary vessels [15–18]. Thanks to this technique the Dmax and Dmean for the LAD decrease by approximately 50–60%. This is a very useful form of therapy, but also very time consuming and the capacity is lower as well. Moreover, this form of therapy forces a patient to maintain strict cooperation during the entire treatment process, which is sometimes difficult or even impossible.

Blank et al. [19] reported that the time span between entering the apparatus and administering the first fraction of treatment with slow breathing was, on average, 42 minutes, whilst the time span of conventional treatment was 15 minutes [19].

Our observations show that in patients with a larger quantity of fatty tissue and a thicker chest wall, the dose deposited on the LAD area was lower than in the case of persons with a thin chest wall and/or smaller amount of the fatty tissue. Similar observations were made by Tanaka et al. [9]. In patients with a lower body mass index, a thinner chest wall and a small amount of fatty tissue in the pericardium, the irradiation dose for the LAD was higher than in patients with larger amounts of pericardial fatty tissue which isolated the LAD from the chest wall, increasing the distance between them. In multivariant analysis, BMI was significantly correlated with Dmax, V 20 Gy and V 30 Gy. In patients with BMI $\leq$22 kg/m^2 and with BMI >22 kg/m^2 there were significant differences in the Dmean and V 40 Gy doses[9].

In the study of Niedere et al. [20] the average LAD volume was 1.94 cm (1.28–2.86). Planning was carried out with the use of 3D and IMRT techniques. As in some patients, PTV was very close to the LAD, it was not possible to reduce the dose of irradiation there. In the case of planning with the use of the IMRT technique, the deposited radiation was much lower in comparison with the 3D technique. And thus, in the case of a small LAD volume, 100% of the vessel received the prescribed dose, and with the IMRT technique the reduction of the mean dose was 44%. Maximum accepted doses and volumes for the LAD, adopted by the authors of the study were: a maximum 60% dose for any LAD volume, a 20% dose for 75% LAD volume, a 40% dose for 50% LAD volume and a 50% dose for 20% LAD volume [20].

Conclusions

The contouring of the left anterior descending artery is always difficult, but may reduce the post-radiation side effects, and

therefore may allow for a lower rate of cardiological incidents. Thanks to this process, the treatment planning and execution may be modified on the basis of the LAD location. However, further prospective studies carried out on larger groups of patients are necessary.

Conflict of interest: none declared

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Review article

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Adjuvant radioiodine treatment in patients with thyroid cancer – current recommendations

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Radioactive iodine therapy (RAI) has been used in patients with differentiated thyroid cancers (DTC) for many decades. However, many changes in thyroid cancer treatment have been introduced for the last decade worldwide, mainly a tendency to deescalate both surgical and adjuvant treatment has been observed. This work summarizes current Polish guidelines for adjuvant radioiodine therapy compared to American Thyroid Association recommendations.

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Key words: radioiodine treatment, thyroid cancer

Radioactive iodine (RAI) has been used for the postsurgical treatment of differentiated thyroid cancer (DTC) for over 50 years. Its therapeutic application in DTC is related to the ability of thyroid cells (both normal and cancerous) to actively capture iodine, including RAI, which is a β radiation emitter [1]. The incorporation of RAI into a thyrocyte cell leads to the formation of free radicals that damage the DNA structure and contribute to cell death or loss of its growth and division potential. For many years, radioiodine treatment was routinely recommended as an adjunct to surgery regardless of the disease recurrence or death risk.

The last decade has introduced many changes related to DTC treatment. With the development of new diagnostic methods, such as thyroglobulin (Tg) measurement or ultrasound examination, as well as better understanding of the biology and natural history of DTC, routine post-surgical radioiodine treatment has been questioned. A tendency to deescalate both surgical and adjuvant treatment has been observed [2]. However, the targets of adjuvant ^{131}I have remained unchanged and include the following:

- ablation of residual normal thyroid tissue, which may facilitate surveillance,
- 'adjuvant therapy' due to a potential tumoricidal effect on residual microscopic RAI-avid disease,
- the possibility of detection of unknown local or distant metastases in a post-treatment whole-body scan.

While all the above targets are important, the ultimate endpoint of postsurgical ablation is to minimise DTC recurrence and death, primarily by eliminating residual normal thyroid tissue or residual microscopic disease.

In patients with structural disease, particularly in patients with non-resectable disease or after a non-radical operation (R2) or with distant metastases, radioiodine therapy is not adjuvant treatment. In these cases, the target of radioiodine therapy is complete disease remission or palliative intension. There are no indications for radioiodine treatment in patients with anaplastic or medullary thyroid cancer.

Of note, treatment recommendations for DTC radioiodine therapy have changed over time and vary among countries. While American Thyroid Association (ATA) guidelines have become more and more restricted regarding the use of radioiodine, other countries, including Poland, are more open to recommending radioiodine therapy [3–5]. The main reason for this discrepancy is the lack of prospective randomised trials in DTC radioiodine

treatment. Outside the radioiodine-refractory DTC setting, only two prospective randomised trials have been published [6, 7]. They are, however, related to the preparation for RAI therapy or RAI activity rather than to the indications for such therapy.

Eligibility for adjuvant ^{131}I treatment in DTC is mainly based on a 3-stage recurrence risk classification (Tab. I) developed by the ATA [2]. The TNM classification alone is no longer sufficient and hence a detailed histological assessment is necessary. It should include information related to the size of the primary lesion, multifocality, histological subtypes of the cancer, the presence and the extent of the extrathyroid infiltration, angioinvasion and the assessment of the number and the diameter of lymph node (micro/macro) metastases. In the future, the diagnosis of the molecular status of the tumour (i.e. the presence of the mutation of increased risk of unfavourable disease course such as *BRAF* or *TERT*) may be necessary. However, currently it is not routinely considered at the time of patient eligibility for adjuvant treatment. Other significant factors for such therapy also include the measurement of postoperative Tg concentration.

Although the ATA recurrence risk scale (Tab. I) was accepted in Europe and Poland, its interpretation is different compared to the USA, particularly in patients from the intermediate recurrence risk group [5]. Both Polish and American guidelines stress the necessity of adjuvant radioiodine treatment in patients from the high risk group in whom histological findings revealed extrathyroid infiltration (pT4), the diameters of metastases ≥3 cm and angioinvasion of more than 4 vessels in follicular thyroid carcinoma or if high postoperative concentration of Tg is found [2, 4].

Adjuvant radioiodine therapy can be abandoned in patients from the low risk group in case of papillary thyroid cancer (pT1a) without other negative risk factors, which is consistent with European and American guidelines (Tab. II). However, in other advancement stages, eligibility for the extent of surgery and adjuvant radioiodine therapy is open to debate.

According to the ATA 3-stage recurrence risk classification, patients with lymph node micrometastases (<2 mm in diameter) whose number does not exceed 5 are included in the low risk group and radioiodine therapy is not routinely recommended. However, Polish guidelines recommend adjuvant RAI treatment in all patients with lymph node metastases irrespective of their diameter, number or location (pN1a, pN1b) (Tab. II, III).

According to the ATA, patients staged pT1b-T2N0 are included in the low risk group and in this case the ATA recommends lobectomy without adjuvant ^{131}I treatment.

Currently in Poland, lobectomy is only performed in patients staged cT1aN0M0, as opposed to ATA recommendations [4]. In Poland, as in other European countries, patients staged pT1b-T2N0M0 receive adjuvant radioiodine treatment considerably more often.

Obviously, one of the reasons for such management is the different extent of surgical treatment (total or near-total thyroidectomy), the different courses of the disease, depending on the region of the world and the very good results of such management reported in European countries.

According to the Polish recommendations, adjuvant radioiodine therapy may be abandoned in patients staged pT1b-T2N0M0 if negative prognostic factors (e.g., aggressive histological subtype or angioinvasion) were not found postoperatively and the potential benefits of such management outweigh the risk of recurrence [4].

Similarly, differences are also noted in terms of recommendations for adjuvant therapy in patients from the intermediate risk group (Tab. III). In Poland, these patients are routinely qualified for ^{131}I treatment, while in the United States abandonment of RAI treatment is permissible.

Table I. 3-stage recurrence risk classification of differentiated thyroid cancers based on the 2015 American Thyroid Association Guidelines [2]

Low risk group	Intermediate risk group	High risk group
Papillary thyroid cancer with all of the following: – no local or distant metastases; – total macroscopic tumour resection; – no extrathyroid extension; – no aggressive histology of tumour (e.g., tall cell, hobnail variant, columnar cell carcinoma); – no vascular invasion; – clinical N0 or <5 pathologic N1 micrometastases (<0.2 in largest dimension); – if ^{131}I is given, there are no RAI-avid foci outside the thyroid bed on the first posttreatment whole-body scan. Intrathyroidal, well differentiated follicular thyroid cancer without capsular or vascular invasion or minimal (<4 foci) vascular invasion. Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutation.	– microscopic invasion of tumour into the perithyroidal soft tissues; – aggressive histology; – papillary thyroid cancer with vascular invasion; – clinical N1 or >5 pathologic N1 with all involved lymph nodes (0.2–3 cm in dimension); – multifocal papillary microcarcinoma with extrathyroid extension and the presence of BRAFV600E mutation; – if ^{131}I is given, there are RAI-avid foci outside the thyroid bed on the first posttreatment whole-body scan.	– gross extrathyroid extension; – incomplete tumour resection; – distant metastases; – postoperative serum thyroglobulin level suggestive of distant metastases; – pathological N1 with any metastatic lymph node ≥3 cm in largest dimension; – follicular thyroid cancer with extensive vascular invasion (>4 foci).

Table II. Comparison of recommendations for adjuvant radioiodine treatment in patients from the low risk group based on Polish and American recommendations [2, 3]

Advancement		Strength of recommendation	ATA 2015 guidelines	Polish 2018 guidelines
T1a N0 (x) M0 (x)	lesion ≤1 cm unifocal multifocal	strong weak	no no	no no
T1b, T2 N0 (x) M0 (x) micro N1 M0 (x)	lesion(s) of 1–4 cm with no lymph node metastases or with the presence of lymph node micrometastases, with no distant metastases and with no other negative prognostic factors found in histological examination	weak	selectively	therapy can be abandoned after the assessment of postsurgical treatment (not applicable to patients with N1)

Table III. Comparison of recommendations for adjuvant radioiodine treatment in patients from the intermediate risk group based on Polish and American recommendations [2, 3]

Advancement		Strength of recommendation	ATA 2015 guidelines	Polish 2018 guidelines
T3 N0 (x)	lesion >4 cm	weak	consider	yes
T3 N0 (x)	extrathyroid extension	weak	consider/rather yes	yes
T1–3 N1a	central lymph node metastases	weak	consider/rather yes	yes
T1–3 N1b	lateral lymph node metastases	weak	consider/rather yes	yes

Eligibility for ^{131}I adjuvant treatment is related to time after surgery and thyroid remnant volume. Radioiodine treatment should be performed at the earliest about 4 weeks postoperatively when the wound has healed, the postoperative oedema has resolved, and the Tg level has decreased. According to the Polish recommendations, therapy should be performed within 9 months after surgery, and when this period exceeds 9–12 months, the treatment is considered delayed. Indications for adjuvant radioiodine treatment 12 months after surgical procedure is questionable [4].

Large thyroid remnants (>1 ml on either site of the thyroid bed) are relative contraindications for radioiodine adjuvant treatment, since with large thyroid remnants treatment success rate is worse. Higher or repeated RAI activities are necessary, which results in increased RAI therapy-related risks [4].

A high level of thyroid stimulating hormone (TSH) is essential for RAI uptake by thyroid cells. Traditionally, a high level of TSH has been achieved by withholding thyroxine therapy for 4–6 weeks after surgery. As a result, hypothyroidism can affect the quality of life of patients and lead to the imbalance of several biochemical parameters, particularly in the elderly. Recombinant human TSH (rhTSH) was developed to facilitate RAI application without withholding thyroxine. In most Polish radioiodine treatment centres, rhTSH is the preferred method of TSH stimulation. Therefore, there is no need to delay L-thyroxine therapy in patients after thyroid surgery.

To conclude, in Poland postoperative radioiodine therapy is given to patients:

a) from the high and intermediate risk groups
b) from the low risk group if:
   - lymph node micrometastases are found in the postoperative histological examination,
   - an increased concentration of Tg is found postoperatively (stimulated Tg level >10 ng/dl),
   - iodine accumulation is observed outside the thyroid bed.

Conflicts of interest: none declared

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Case report

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The atypical form of granulomatous lobular mastitis – diagnostic dilemmas. A case report

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Idiopathic granulomatous mastitis (IGM) is a chronic inflammatory condition that may cause diagnostic difficulties during clinical tests and radiological examinations in terms of differentiation from contagious diseases, such as tuberculosis (TB) and fungal infections, as well as cancer. This report presents the case of a 23-year-old woman with granulomatous mastitis, along with a discussion of the diagnostic dilemmas based on a clinical test, mammography, ultrasonography and histopathological examination. IGM produces varied and non-specific manifestations on mammography and ultrasonography. Therefore, histopathological examination is necessary to make an unambiguous diagnosis. The possibility of this condition must always be borne in mind to minimise the risk of an erroneous cancer diagnosis. There are no standard procedures in force for the treatment of IGM.

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Key words: granulomatous mastitis, breast cancer

Introduction

IGM is a rare, benign and chronic inflammatory condition of the breasts, which affects women of childbearing age [1, 2]. The first description of the disease was presented in 1972 by Kessler et al. to define granulomatous mastitis with an unknown etiological agent [3]. In 1987, Going et al. recommended the term 'granulomatous lobular mastitis' (GLM) to differentiate the lesion from granulomatous periductal mastitis [4]. The lesion was described as granulomatous mastitis affecting the breast lobule and leading to its destruction. The granulomas were made up of histiocytes, Langhans giant cells, lymphocytes and plasmacytes. Granulomas do not undergo caseous necrosis. Over time, the lesions may form confluent structures with fat tissue necrosis, abscess formation and fibrosis. Selective tests fail to reveal any microorganisms and the lesions contain no foreign bodies. Occasionally, it is possible to observe focal lesions related to lactation in women who have recently been pregnant. Differential diagnostics also encompass other granulomatous lesions. Differentially diagnosing with tuberculosis, sarcoidosis and cat-scratch disease (CSD) is most often performed on the basis of clinical and histopathological images [5,6]. This process must always take into account granulomatous mastitis, which accompanies infiltrating or *in situ* breast cancer [7, 8].

Case report

A 23-year-old female patient reported to the Oncological Surgery Outpatient Clinic due to a tumour in the left breast, which she had discovered about 1.5 months earlier. No other present or past diseases were reported during history taking.

Three years earlier, she had given birth naturally to one child and breast-fed for six months. The patient reported no family history of cancers, and did not suffer from fever, lung diseases, dental problems, facial skin lesions, tonsillitis, gingivitis or breast injuries. Physical examination of the left breast, within the external quadrants, revealed a palpable tumour of 8 x 8 cm in diameter, which was hard and rough, poorly mobile, and produced no lesions on the skin above it. In the left axillary fossa, there were single enlarged and mobile lymph nodes. Clinically, the lesion aroused suspicion of a cancerous growth.

A blood test revealed mild leukocytosis (white blood cell [WBC] count: 10 100) and increased C-reactive protein concentration (176 mg/l, <10 mg/l). No abnormalities were shown in the patient's chest X-ray.

A breast X-ray revealed an area of irregular structure in the external quadrants on the left side, measuring 8 x 8 cm, with strong local vascularisation and local micro-calcifications (BIRADS-5). In the bottom and middle parts of the left axilla (armpit), there were four completely hypoechogenic lymph nodes and one with a cortex thickened to 6 mm. These were U4-type nodes (Fig. 1).

Contrast-enhanced spectral mammography revealed a non-homogeneous, irregular infiltration measuring 11 x 6 cm in the left breast and abnormal lymph nodes of 10 mm in short-axis view in the left axillary fossa. The right breast showed no radiologically suspicious changes (BIRADS-5) (Fig. 2).

An ultrasound-guided core-needle biopsy (CNB) was performed. The histopathological examination of the specimen revealed severe, chronic active breast inflammation (mastitis). The connective tissue stroma showed the presence of tiny necrotic foci. The entire specimen contained numerous visible inflammatory granulomas made up of epithelioid cells, mainly multinucleate giant cells. No necrosis was found in any of the granulomas. Minor reactive lesions were observed within the ductal epithelium. A cytokeratin (CK) immunohistochemical study was performed to confirm the presence of potential cancer infiltration cells. However, the result of this study excluded the presence of cancer cells in the specimen (Fig. 3).

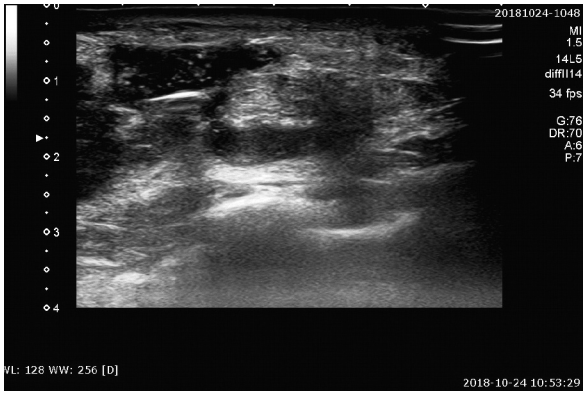

Figure 1. Ultrasonography of the left breast

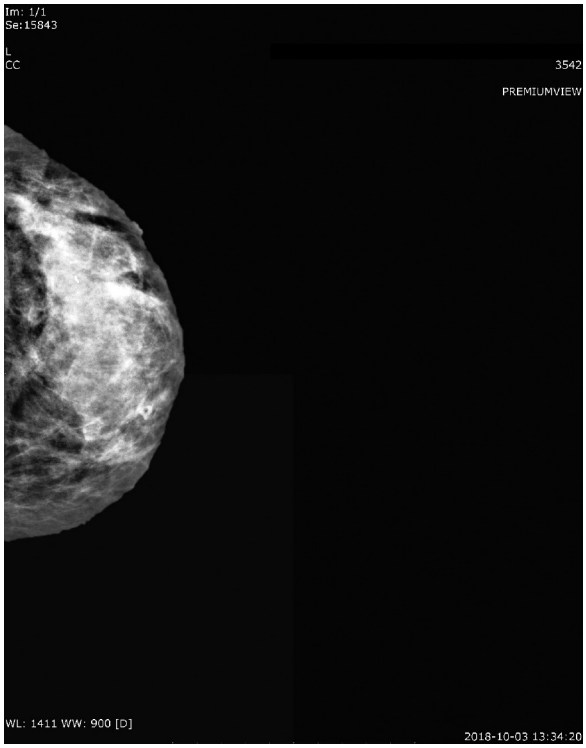

Figure 2. Spectral mammography of the left breast

No cancer cells were found on fine-needle aspiration biopsy (FNAB) of the lymph nodes.

Seven days after CNB, numerous hard, erythematous and suppurative foci appeared over the tumour (Fig. 4).

Swabs were taken from the lesions, but the bacterial cultures from the skin and the purulent secretion for *Actinomyces* and *Nocardia* were negative.

Since the clinical picture might have suggested actinomycosis, a pathologist was asked to search for the characteristic "sulphuric granules". The specimen was therefore dissected and thoroughly examined again. Unfortunately, the histopathological examination of numerous samples stained with hematoxylin and eosin did not confirm the presence of "sulphuric granules" or filamentous bacteria. In order to confirm or finally exclude an *Actinomyces israeli* infection, the Gram staining technique was used, yet did not confirm the presence of Gram-positive bacteria. Fungal infection was also excluded based on an assessment of Grocott-stained specimen samples. Ziehl-Neelsen staining, which was performed on mycobacteria, yielded a negative result. The granulomas revealed no presence of the caseous necrosis typical of TB. Since an etiological factor was not found, the case in question was assumed to be granulomatous mastitis.

The patient was started on oral Amoxicillin at a dose of 1g twice a day, for the first month. Next, the therapy was reduced to 1g once a day. After six months of the therapy, the tumour was no longer palpable, the skin lesions had decreased and the filtration subsided. After the following three months, the skin lesions disappeared. The patient remains under observation.

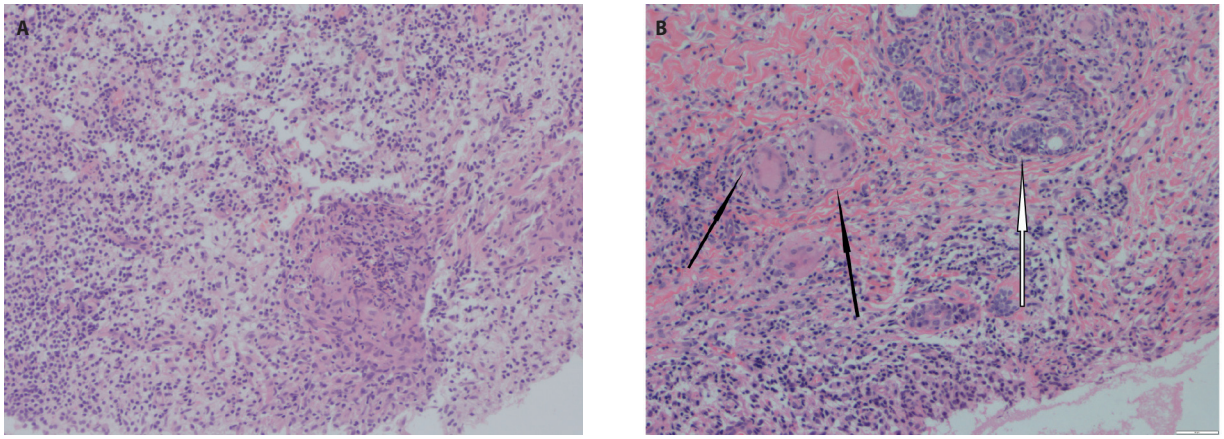

Figure 3. Mixed lympho-granulocytic inflammatory infiltrate with non-necrotic granuloma (A). Non-necrotic granuloma with multinucleate giant cells (the black arrow) and a breast lobule (the white arrow), HE, magn. 100x (B)

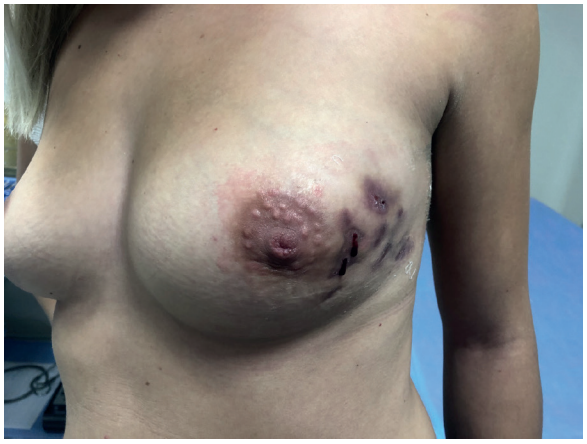

Figure 4. The left breast 7 days after CNB

Discussion

Idiopathic granulomatous mastitis is a rare, chronic inflammatory condition of the breasts, primarily observed in women of childbearing age. Its precise etiology is not known. One hypothesis is that it is caused by autoimmune factors or associated with lactation [9, 10].

The dominant feature is most commonly a tumour, usually with a cohesive texture, which may be accompanied by pain, reddening and enlarged lymph nodes [10]. As the disease progresses, there are other manifestations such as pulled-in nipples, reddening, ulceration and fistulas, which may lead to erroneous diagnoses of infiltrating breast cancer [11, 12].

Imaging examinations of IGM, such as mammography and ultrasonography, are non-specific and may often be mistakenly interpreted as cancer. In the case at hand, the tumour lesion in the breast was classified as BIRADS-5 on both mammography X-ray and ultrasonography. Some authors suggest performing magnetic resonance imaging (MRI) in IGM diagnostics. However, studies have revealed that MRI provides no additional data helpful in differentiating between IGM and breast cancer.

Due to the ambiguous IGM assessments from clinical and imaging examinations, diagnosis should be based on a histopathological analysis following CNB or tumorectomy [4, 11, 12]. Besides infiltrating cancer, differential diagnostics should also take into consideration other chronic inflammatory breast conditions, such as plasma cell inflammation, histoplasmosis, tuberculosis and Wegener's granulomatosis [13].

The treatment of idiopathic granulomatous mastitis is diverse, and the therapeutic options include conservative treatment with an antibiotic, corticosteroid therapy or wide local excision (WLE). A study by Atak et al. revealed that the best treatment method for IGM patients involved surgical excision combined with the administration of steroids [14].

Similarly, in a study by Sheybani et al. conducted on twenty-two IGM patients, surgical treatment was the treatment of choice [15]. In a study by Mahmodlou et al., steroid therapy as a therapeutic method was found to be an effective treatment method for IGM as it reduced inflammation [16]. Our patient was started on antibiotic therapy for six months, resulting in withdrawal of the symptoms.

The condition produces varied and non-specific manifestations on mammography and ultrasonography. Histopathological examination is therefore necessary to make a diagnosis. However, the possibility of IGM must always be borne in mind to minimise the risk of an erroneous cancer diagnosis. There are no standard procedures in force for the treatment of IGM.

Conflict of interest: none declared

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The authorship of research results and scientific publications in medical sciences

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Introduction. The article aims to present the rules for determining the authorship of research results and scientific publications under intellectual property law and the applicable standards.

Materials and methods. The study is based on copyright law, national and international codes of ethical conduct in research and scientific publications, including the European Code of Conduct for Research Integrity and the guidelines for publication in medical journals of the International Committee of Medical Journal Editors.

Results and discussion. The standards for the attribution of authorship to scientific results under intellectual property law, the applicable guidelines and customs are not consistent. Strict rules for determining the status of an author based on their creative contribution within the meaning of copyright law do not correspond in full extent to the needs of the sciences, where almost every contribution to research, clinical trials, and the preparation of publications is appreciated. In practice, this may create conflicting situations as to the proper identification and indication of authorship and co-authors.

Conclusions. Among the standards for recognizing authorship, copyright standards prevail. A compromise solution between the restrictive approach for attributing authorship (co-authorship) of works under copyright and the non-binding recommendation of the ethical codes, is to distinguish between the 'authors' and other 'non-authors' who contributed to the creation of work, thereby protecting the interests of all parties involved.

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Key words: authorship of research results, authorship of publications, co-authorship, plagiarism

Introduction

Although medicine and the healthcare system are increasingly subject to the standards of various areas of law (e.g. medical, pharmaceutical, personal data protection regulations), intellectual property law does not seem to be particularly relevant to these areas. This conclusion is not entirely appropriate. Firstly, patents and know-how are an essential tool for the protection of medicinal products, devices and methods for medical treatment. Secondly, publications containing the results of research work, or clinical trials in various fields of medicine are subject to copyright protection. This justifies even brief commentary on some problems in this field of law, even in medical journals.

Among the issues selected from the field of intellectual property covered by the series of articles "Intellectual Property Rights and Medicine", the problem of authorship and co-authorship of research results and publications is of importance in the field of research in medical science. Against this background, controversies and possible conflicts derive from a number of sources. First of all, there is the different understanding of creativity and authorship in sciences, and this based on intellectual property law. Secondly, various standards are provided under intellectual property law and the applicable national, international codes of ethics for research and scientific activities, as well as publication guidelines and recognized customs for attributing authorship.

Materials and methods

Determining guidelines for authorship (or co-authorship) and situations in which infringement of intellectual property rights

concerning authorship occur, requires the identification of the legal grounds appropriate for further analysis. It includes brief comments of what constitutes the subject of protection under intellectual property law and, consequently, who enjoys the moral right to the authorship of such intellectual creations.

Intellectual creativity and authorship, which have significant scientific, social and financial consequences, are immaterial goods protected as the personal rights of a natural person under the provisions of the Civil Code and as copyright rights by the Act on Copyright and Related Rights of 1994 [1].

The object of copyright is any manifestation of creative activity of an individual nature, established in any form, irrespective of its value, purpose or form of expression (work). In the field of research and scientific creations, these can be scientific articles, medical opinions, conference speeches, presentations, posters, databases. The possibility of qualifying an intellectual creation as a copyright work derives from the individual mode of expression of that work. The individual and original character of the work is understood as non-standard, unconventional, not resulting from predetermined requirements, but not its substantive, scientific, economic value, which are essential criteria of creativity relevant to the sciences. Copyright protection starts from the moment of expression of the work in any form (e.g. the oral communication of a conference presentation, an article saved in a computer memory). It also applies to unfinished works, fragments of works (e.g. an abstract of an article, a draft version of a scientific paper).

The criteria used for the assessment of the individual character of a work are liberal, and sometimes even trivial manifestations of intellectual creativity enjoy copyright protection. Meanwhile, copyright law discriminates against creativity in the area of the sciences, where the critical intellectual value is attributed to discoveries, new methods, pure research results, rather than the form and manner of their presentation or expression [2]. These creations 'as such', even when of significant scientific or practical importance, are explicitly excluded from protection by copyright law. According to Article 2^1 of the Polish Copyright Act, protection may apply to the form of expression only and no protection shall be granted to discoveries, ideas, procedures, methods and principles of operation as well as mathematical concepts.

This means that even a short, written description of, for example, the symptoms of cancer can be copyright protected. At the same time, breakthrough research results of a cancer treatment expressed in the form of numerical parameters or an innovative method of a cancer treatment won't enjoy copyright protection. Excluding such results from the protection of exclusive rights under intellectual property law presupposes that the creation of a monopoly on them would restrict freedom of research, access to results and technological progress [3].

The right to authorship of a work and signing it with one's name is one of the author's moral rights that should be distinguished from the economic rights giving the author (or the entity which acquired copyright) the exclusive right to exploit the work. Contrary to these copyright economic rights, which may be contractually transferred to another party, the moral right to authorship cannot be transferred or renounced. Another person or institution (e.g. a publisher) may be only authorized to exercise this right, for example by not signing the work with the author's name or using a special form of indicating the authorship.

The right to authorship of a work is vested in the author (an individual) who created the work. Authorship can be attributed to one or more persons (co-authors). Unfortunately, there is no binding definition of a "co-author", which leads to many disputes over co-authorship. Copyright law takes a restrictive approach to who can be a co-author. To be recognized as a co-author, a person must make "a creative contribution" to the creation of a work. For example, co-authors of a scientific article within the meaning of copyright law will be persons who "physically" prepared (wrote) such a paper, created its plan, layout, decided on a specific argumentation, formulated conclusions. In contrast, persons whose contribution to the common understanding is also significant are not considered authors in the sense of intellectual property law. For example, authors of the concept of the publication itself, the persons who have conducted research, obtained results, have been consultants, have made a substantive assessment or editorial corrections, have managed the research work or the project which resulted in its publication).

Copyright law does not "value" the authorship of a work in any way, i.e. there are no rules regarding placing the names of authors in any particular order (e.g. the leader of the research team as the first-mentioned author, other authors, etc.). The amount of creative contribution reflects shares in economic copyright rights to the work.

Authorship is a matter of fact: i.e. it results only from the point of creating a work or making a creative contribution within the meaning of copyright law. On the one hand, indicating someone as the author of a work (e.g. a publication), or including them in an agreement concerning the exploitation of the work (e.g. a publishing agreement), does not make such a person an "author" within the meaning of copyright law. On the other hand, given that copyright protection arises without any formalities (so that sometimes it may be challenging to prove being the author of a work) copyright law provides the so-called presumption of authorship. It considers as the author (co-author) a person whose name appears on a copy of the work (e.g. a hard copy of the manuscript) or whose name is communicated to the public in connection with the dissemination of the work (e.g. is mentioned at a conference as the presenter of a lecture). The presumption of authorship is advantageous in the case of a dispute on copyright infringement. Until a third party proves the person indicated as the author has not factually created the work, everybody must consider

the person stated on the work as being its author. Therefore, it is essential to remember to sign works with one's own name, and also indicate the fact when verbal communication of copyright works to the public takes place.

In addition to copyright standards, the proper indication of the authors of research results and scientific publications is the subject of various non-binding recommendations and codes of ethics, which introduce different rules on authorship than those indicated above.

Liberal standards in this respect are provided, for example, by the European Code of Conduct for Research Integrity [4]. The Code includes the possibility of attributing authorship and indicating the order of the author according to the assumption that the status of an author results from their significant participation in the planning of research, the collection of data or their interpretation. This ethical code also introduces a requirement for publishers and reviewers of publications to respect authorship in obtaining authors' consent to use their ideas, data, research results or the further interpretation of them.

At the national level, one example is the Code of Ethics for Researchers developed by the Commission on Ethics in Science [5]. It has been adopted by the General Assembly of the Polish Academy of Sciences in 2016 and is also used by many institutions in the field of medical science (e.g. medical universities, the Medical Centre for Postgraduate Education). In terms of copyright and publishing practices, this Code contains recommendations that the authorship of a scientific publication should be based solely on a creative and substantial contribution to the research. However, it defines the relevant contribution differently from copyright law, namely as a contribution consisting of significant participation in initiating a scientific idea, creating a concept and design, research, substantial involvement in data acquisition, analysis and interpretation of the results obtained, as well as a significant contribution to the drafting and writing of an article or the critical improvement of it in terms of intellectual content. The Code of ethics recognizes plagiarism as one of the forms of the offensive violation of ethical principles in science. It defines this broadly as an action consisting of the appropriation of someone else's ideas, research results or statements without correctly stating the source. Even though according to the Code it constitutes a violation of intellectual property rights, such a definition does not correspond to the understanding of plagiarism under copyright law, which can only be committed with regards to content which is protected by copyright. Since copyright does not protect the ideas or results themselves, but only the form the author uses to describe them, using somebody's else's results is not plagiarism in the legal sense, but can still be questioned as an infringement of the personal right to scientific creativity.

Autonomous recommendations for determining who is an the author, directly related to publications in medical journals, include the recent recommendations of the International Committee of Medical Journal Editors, called the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of 2019 [6]. These recommendations recognize the author of a publication as a person who meets the following conditions cumulatively:

1. has made a significant contribution to the concept or design of the paper, obtaining, analyzing or interpreting the data covered by the work;
2. elaborated and critically explained the relevant content;
3. has approved the final version of the work;
4. was responsible for the correctness and accuracy of the presented content.

Consequently, persons who do not meet all the conditions indicated should not be reported as authors. The conditions defined in this way are not consistent with the requirements of copyright law, where for the recognition of authorship, the activities mentioned in point 2 and 3 are relevant and sufficient. According to the recommendations it is appropriate to indicate persons who performed auxiliary functions in the preparation of the work (e.g. performed general supervision over the research group, participated in the editing of the work and linguistic correction), but as a category separate from the authors (e.g. as "participating researchers").

Results and discussion

Copyright law protects the form of expression and surprisingly not the substantive, scientific or applicable content. Thus, the intellectual property system does not meet the needs of the sciences, where the persons responsible for discoveries, those developing scientific methods, generating valuable experimental data are traditionally also considered authors. Confusions regarding authorship even deviate from the conviction that the author is someone whose contribution was not only substantially, but also scientifically and organizationally essential for the research and published results. The lack of consistency between copyright standards for the recognition and protection of authors and guidelines provided by the codes of ethics and recommendations for scientific publications creates situations in which the authorship may be disputable. On the one hand, it may be controversial to include among the authors persons who do not contribute creatively to the copyright work creation (within the meaning of this regime) or in opposition to recognize as authors, those who only participated in the research and obtained the results included in the work. On the other hand, because of the possibility of being accused of infringing the right to authorship and committing plagiarism, the names of those have contributed creatively to the creation of the work and are co-authors according to copyright law should not be omitted.

Conclusions

Disputes about authorship in the field of scientific research and publication, allegations of plagiarism, the unreliable use and misleading indication of research are increasingly common

and medical science does not bypass them. The following guidelines can help to avoid this problem.

First of all, a distinction must be made between authorship (or co-authorship) of work as a protected copyright moral right and attributing the name of the author (or co-author) based only on their substantive or organisational involvement in conducting the research, obtaining results, or preparing publications. The rules for recognizing authorship within the meaning of intellectual property law should, in any case, prevail and should respect the actual creative participation in creating the work. Misappropriation of authorship by taking over fragments of another author's work without proper indication of who is an author, as well as the misrepresentation of a part of or the whole of someone else's work, constitutes an infringement of personal copyright in the form of plagiarism, threatened by civil liability (Article 79 of the Copyright Act) and criminal liability (Article 115 of the Copyright Act).

Secondly, ideas, discoveries, pure research data, which are not protected as such by intellectual property rights, are scientific creations protected as personal rights. The use of these kinds of intellectual achievements without identifying the persons from whom they derive does not constitute plagiarism within the meaning of copyright law, but may still be questioned as an infringement of the personal right to scientific creation under Article 23 and 24 of the Polish Civil Code.

Thirdly, to avoid infringing the principles of ethics in conducting research and scientific activities, the gap resulting from the restrictive definition of co-authors under copyright standards should be filled by identifying all the persons who participated in the research and not omitting their contribution. The researchers involved should be indicated in a different category from the authors with an appropriate annotation (e.g. "involved in research", "served as a scientific adviser", "critically reviewed a research proposal", "collected data", "provided and cared for the patients examined", "participated in the editing of publications"). Persons who contributed in this way are not entitled to authorship as a moral copyright right and do not enjoy its protection under copyright law. The omission of their names among the 'authors' does not formally constitute copyright infringement but can be targeted as an infringement of the ethical standards of scientific activity.

Fourthly, if many researchers are involved in preparing a publication, it might not be very easy afterwards to determine the contribution and authorship relevant for being recognized as an author. Therefore, the recommendation is to record all activities from the early stages, which allows the identification of the group of co-authors of the work and the persons participating in its preparation following their factual contributions, and possibly to avoid future disputes over authorship and copyright infringement.

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